(19) World Intellectual Property Organization International Bureau



(43) International Publication Date 31 October 2002 (31.10.2002)

PCT

(10) International Publication Number WO 02/086085 A2

(51) International Patent Classification7:

...

(21) International Application Number: PCT/US02/12801

(22) International Filing Date: 24 April 2002 (24.04.2002)

(25) Filing Language:

English

C12N

(26) Publication Language:

English

(30) Priority Data: 60/285,683

24 April 2001 (24.04.2001) US

- (71) Applicants (for all designated States except US): BAYER CORPORATION [US/US]; 100 Bayer Road, Pittsburgh, PA 15205 (US). MORPHOSYS AG [DE/DE]; Lena-Christ-Str. 48, 82152 Martinsried/Munchen (DE).
- (72) Inventors: and
- (75) Inventors/Applicants (for US only): PAN, Clark [US/US]; 22362 Princeton Place, Castro Valley, CA 94552 (US). KNORR, Andreas, M. [DE/DE]; Trillser Graben 10, 40699 Erkrath (DE). SCHAUER, Michael [DE/DE];

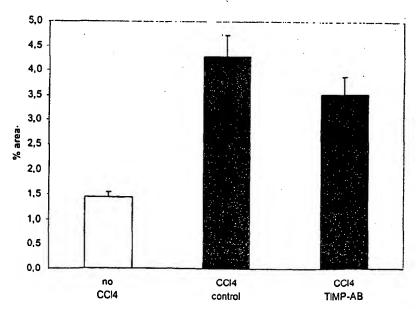
Falkenberg 28, 42113 Wuppetatal (DE). HIRTH-DIET-RICH, Claudia [DE/DE]; Stockmannsmühle 127, 42115 Wuppertal (DE). KRAFT, Sabine [DE/DE]; Planegger Strasse 11 A, 82152 Planegg (DE). KREBS, Barbara [DE/DE]; Auf Dem Kamm 13, 51427 Bergsich Galdbach (DE).

- (74) Agent: HEMMENDINGER, Lisa, M.; Banner & Witcoff, Ltd., 11th floor, 1001 G Street, N.W., Washington, DC 20001-4597 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,

[Continued on next page]

(54) Title: HUMAN TIMP-1 ANTIBODIES

Morphometry



(57) Abstract: Human antibodies that bind to TIMP-1 can be used as reagents to diagnose and treat disorders in which TIMP-1 is elevated, such as liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, colon cancer, lung cancer, and idiopathic pulmonary fibrosis.



GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

 without international search report and to be republished upon receipt of that report

HUMAN TIMP-1 ANTIBODIES

[01] This application claims priority to and incorporates by reference co-pending provisional application Serial No. 60/285,683 filed April 24, 2001.

FIELD OF THE INVENTION

[02] The invention relates to TIMP-1-binding human antibodies.

BACKGROUND OF THE INVENTION

- [03] Tissue inhibitors of metalloproteases (TIMPs) inhibit metalloproteases, a family of endopeptide hydrolases. Metalloproteases are secreted by connective tissue and hematopoietic cells, use Zn²⁺ or Ca²⁺ for catalysis, and may be inactivated by metal chelators as well as TIMP molecules. Matrix metalloproteases (MMPs) participate in a variety of biologically important processes, including the degradation of many structural components of tissues, particularly the extracellular matrix (ECM).
- [04] Degradation of extracellular matrix tissue is desirable in processes where destruction of existing tissues is necessary, e.g., in embryo implantation (Reponen et al., Dev. Dyn. 202, 388-96, 1995), embryogenesis, and tissue remodeling. Imbalance between synthesis and degradation of matrix proteins, however, can result in diseases such as liver fibrosis (Iredale et al., Hepatology 24, 176-84, 1996). This imbalance can occur, for example, if levels of TIMPs are increased. Disorders in which TIMP-1 levels of increased include, for example, liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, and colon cancer. See, e.g., Inokubo

et al., Am. Heart J. 141, 211-17, 2001; Ylisirnio et al., Anticancer Res. 20, 1311-16, 2000; Holten-Andersen et al., Clin. Cancer Res. 6, 4292-99, 2000; Holten-Andersen et al., Br. J. Cancer 80, 495-503, 1999; Peterson et al., Cardiovascular Res. 46, 307-15, 2000; Arthur et al., Alcoholism: Clinical and Experimental Res. 23, 840-43, 1999; Iredale et al., Hepatol. 24, 176-84, 1996.

[06] There is a need in the art for reagents and methods of inhibiting TIMP-1 activity, which can be used to provide therapeutic effects.

BRIEF SUMMARY OF THE INVENTION

- [07] It is an object of the present invention to provide reagents and methods of inhibiting TIMP-1 activity. This and other objects of the invention are provided by one or more of the embodiments described below.
- [08] One embodiment of the invention is a purified preparation of a human antibody, wherein the antibody binds to a tissue inhibitor of metalloprotease-1 (TIMP-1) and neutralizes a matrix metalloprotease (MMP)-inhibiting activity of the TIMP-1.
- [09] Another embodiment of the invention is a purified preparation of a first human antibody which comprises a VHCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360.
- [10] Still another embodiment of the invention is a purified preparation of a first human antibody which comprises a VLCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379.
- [11] Yet another embodiment of the invention is a purified preparation of a first human antibody which has TIMP-1 binding and MMP-inhibiting activity characteristics of a second human antibody. The second antibody comprises a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NOS:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5

and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

Even another embodiment of the invention is a purified preparation of a human antibody comprising a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ

ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

A further embodiment of the invention is a purified preparation of a human antibody [13] which comprises a heavy chain and a light chain amino acid pair selected from the group consisting of SEQ ID NOS:140 and 97, SEQ ID NOS:141 and 98, SEQ ID NOS:142 and 99, SEQ ID NOS:143 and 100, SEQ ID NOS:144 and 101, SEQ ID NOS:145 and 102, SEQ ID NOS:146 and 103, SEQ ID NOS:142 and 97, SEQ ID NOS:142 and 98, SEQ ID NOS:142 and 100, SEQ ID NOS:142 and 101, SEQ ID NOS:142 and 102, SEQ ID NOS:142 and 103, SEQ ID NOS:146 and 97, SEQ ID NOS:146 and 98, SEQ ID NO:146 and 100, SEQ ID NOS:146 and 101, SEQ ID NOS:148 and 104, SEQ ID NOS:148 and 105, SEQ ID NOS:149 and 106, SEQ ID NOS:150 and 107, SEQ ID NOS:151 and 108, SEQ ID NOS:152 and 109, SEQ ID NOS:153 and 110, SEQ ID NOS:154 and 111, SEQ ID NOS:155 and 112, SEQ ID NOS:156 and 113, SEQ ID NOS:157 and 114, SEQ ID NOS:158 and 115, SEQ ID NOS:159 and 116, SEQ ID NOS:160 and 117, SEQ ID NOS:161 and 118, SEQ ID NOS:162 and 119, SEQ ID NOS:163 and 120, SEQ ID NOS:164 and 121, SEQ ID NOS:165 and 122, SEQ ID NOS:166 and 123, SEQ ID NOS:167 and 124, SEQ ID NOS:168 and 125, SEQ ID NOS:169 and 126, SEQ ID NOS:170 and 127, SEQ ID NOS:171 and 128, SEQ ID NOS:172 and 129, SEQ ID NOS:173 and 130, SEQ ID NOS:174 and 131, SEQ ID NOS:175 and 132, SEQ ID NOS:176 and 133, SEQ ID NOS:177 and 134, SEQ ID NOS:178 and 135, SEQ ID NOS:179 and 136, SEO ID NOS:180 and 137, SEQ ID NOS:181 and 138, and SEQ ID NOS:182 and 139.

[14] Another embodiment of the invention is a pharmaceutical composition comprising a human antibody and a pharmaceutically acceptable carrier. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

- Yet another embodiment of the invention is a purified polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [16] Even another embodiment of the invention is a purified polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [17] Still another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- [18] A further embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.
- [19] Another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID

NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

- Yet another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.
- [21] Still another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.
- [22] Even another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182. The heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.
- [23] A further embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain

having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

- [24] Another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139. The light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.
- Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.
- [27] Still another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.

[28] A further embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.

- [29] Another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.
- [30] Still another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182. The heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.
- Yet another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human

antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

- [32] Even another embodiment of the invention is a host cell comprising an expression vector. The expression vector comprises a polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379. The human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1. The human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139. The light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.
- [33] A further embodiment of the invention is a method of making a human antibody. The host cell of claim 43 is cultured under conditions whereby the antibody is expressed. The human antibody is purified from the host cell culture.
- [34] Another embodiment of the invention is a method of decreasing an MMP-inhibiting activity of a TIMP-1. The TIMP-1 is contacted with a human antibody that binds to the TIMP-1. The MMP-inhibiting activity of the TIMP-1 is decreased relative to MMP-inhibiting activity of the TIMP-1 in the absence of the antibody.
- [35] Still another embodiment of the invention is a method of ameliorating symptoms of a disorder in which TIMP-1 is elevated. An effective amount of a human antibody which neutralizes an MMP-inhibiting activity of the TIMP-1 is administered to a patient having the disorder. Symptoms of the disorder are thereby ameliorated.
- [36] A further embodiment of the invention is a method of detecting a TIMP-1 in a test preparation. The test preparation is contacted with a human antibody that specifically binds to the TIMP-1. The test preparation is assayed for the presence of an antibody-TIMP-1 complex.

[37] Even another embodiment of the invention is a method to aid in diagnosing a disorder in which a TIMP-1 level is elevated. A sample from a patient suspected of having the disorder is contacted with a human antibody that binds to TIMP-1. The sample is assayed for the presence of an antibody-TIMP-1 complex. Detection of an amount of the complex which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.

[38] The invention thus provides human antibodies which bind to TIMP-1 and neutralize MMP-inhibiting activity of TIMP-1. These antibodies can be used, *inter alia*, in diagnostic and therapeutic methods.

BRIEF DESCRIPTION OF THE FIGURES

- FIG. 1. Protein sequences encoded by the HuCAL® V_H and V_L Fab master genes. Seven V_H and V_L sequences are aligned, and the approximate location of restriction endonuclease sites introduced into the corresponding DNA sequences are indicated. The numbering is according to VBASE except for the gap in VI position 9. In VBASE the gap is set at position 10. See also Chothia et al. (1992) J. Mol. Biol. 227, 776-798, Tomlinson et al. (1995) EMBO J. 14, 4628-4638 and Williams et al. (1996) J. Mol. Biol. 264, 220-232).
- [40] FIG. 2. Nucleotide sequences of the $HuCAL^{\otimes} V_H$ and V_L Fab master genes.
- [41] FIG. 3. Fab display vector pMORPH® 18 Fab 1.
- [42] FIG. 4. Vector map of pMORPH® x9Fab1_FS.
- [43] FIG. 5. Sequence comparison between human and rat TIMP-1. Sequence regions in bold were used for peptide synthesis. Residues that make stronger direct contacts with MMP-3 are italicized, and residues that make weaker direct contacts with MMP-3 are underlined (Gomis-Ruth et al., 1997).

[44] FIG. 6. Activity of MS-BW-3 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (final conc. 50 μM) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 27% MMP-1 activity (in absence of antibody) as reference values.

- [45] FIG. 7. Activity of MS-BW-44 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (final conc. 50 μM) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 25% MMP-1 activity (in absence of antibody) as reference values.
- [46] FIG. 8. Activity of MS-BW-44, -44-2, 44-6 in human TIMP-1/ MMP-1 assay. Fab antibody fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 0.4 nM), MMP (final conc. 0.4 nM) and peptide substrate (final conc. 50 μM) and incubation for 7 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 55% MMP-1 activity (in absence of antibody) as reference values.
- FIG. 9. Activity of MS-BW-44, -44-2-4, 44-6-1 in human TIMP-1/ MMP-1 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 0.4 nM), MMP (final conc. 0.4 nM), and peptide substrate (final conc. 50 μM) and incubation for 7 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in

material and methods section, using 100% MMP-1 activity (in absence of TIMP-1) and 50% MMP-1 activity (in absence of antibody) as reference values.

- [48] FIG. 10. Binding of Fab fragments to human TIMP-1, -2, -3 and -4. TIMP-1, -2, -3, -4 proteins were immobilized on an ELISA plate, and binding of purified Fab fragments was measured by incubation with alkaline phosphatase conjugated anti-Fab antibody (Dianova) followed by development with Attophos substrate (Roche) and measurement at Ex405nm/Em535 nm.
- [49] FIG. 11. Activity of MS-BW-14, -17, -54 in rat TIMP-1/MMP-13 assay. Antibody Fab fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM), and peptide substrate (to final conc. 50 μM) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-13 (in absence of TIMP-1) activity and 20% MMP-13 activity (in absence of antibody) as reference values.
- [50] FIG. 12. Activity of MS-BW-14 Fab and IgG₁ and MS-BW-3 IgG₁ in rat TIMP-1/MMP-13 assay. Antibodies were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM) and peptide substrate (to final conc.50 μM) and incubation for 1-3 h at 37°C, fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as outlined in material and methods section, using 100% MMP-13 activity (in absence of TIMP-1) and 30% MMP-13 activity (in absence of antibody) as reference values.
- [51] FIG. 13. Activity of MS-BW-17-1 Fab and IgG₁ in rat TIMP-1/ MMP-13 assay. Fab antibody fragments were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM), MMP (final conc. 1.2 nM) and peptide substrate (to final conc.50 μM) and incubation for 1-3 h at 37°C fluorescence at Ex320 nm/Em 430 nm was measured. IC₅₀ was calculated as

- outlined in material and methods section, using 100% MMP-13 activity (in absence of TIMP-1) and 15% MMP-13 activity (in absence of antibody) as reference values.
- [52] FIG. 14. Effect of the inhibitory effect of MS-BW-17-1 TIMP-1 antibody on bleomycin-induced lung fibrotic collagen.
- [53] FIG. 15. Effect of anti-TIMP-1 antibody on fibrotic collagen as stained by Sirus Red in carbon tetrachloride-induced rat liver fibrosis model. Sirius Red-stained area as percent of total field in carbon tetrachloride-treated rats treated with PBS, control antibody, and MS-BW-14 anti-TIMP-1 antibody.

DETAILED DESCRIPTION OF THE INVENTION

[54] The invention provides human antibodies that bind to TIMP-1. These antibodies are useful for a variety of therapeutic and diagnostic purposes.

Characteristics of Human TIMP-1 Antibodies

- [55] "Antibody" as used herein includes intact immunoglobulin molecules (e.g., IgG₁, IgG_{2a}, IgG_{2b}, IgG₃, IgM, IgD, IgE, IgA), as well as fragments thereof, such as Fab, F(ab')2, scFv, and Fv, which are capable of specific binding to an epitope of a human and/or rat TIMP-1 protein. Antibodies that specifically bind to TIMP-1 provide a detection signal at least 5-, 10-, or 20-fold higher than a detection signal provided with other proteins when used in an immunochemical assay. Preferably, antibodies that specifically bind to human and/or rat TIMP-1 do not detect other proteins in immunochemical assays and can immunoprecipitate the TIMP-1 from solution.
- The K_d of human antibody binding to TIMP-1 can be assayed using any method known in the art, including technologies such as real-time Bimolecular Interaction Analysis (BIA) (Sjolander & Urbaniczky, *Anal. Chem. 63*, 2338-45, 1991, and Szabo *et al.*, *Curr. Opin. Struct. Biol. 5*, 699-705, 1995). BIA is a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g., BIAcoreTM).

Changes in the optical phenomenon surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

- In a BIAcoreTM assay, some human antibodies of the invention specifically bind to human TIMP-1 with a K_d of about 0.1 nM to about 10 μM, about 2 nM to about 1 μM, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 0.2 nM to about 13 nM, about 0.2 nM to about 0.5 nM, about 2 nM to about 13 nM, and about 0.5 nM to about 2 nM. More preferred human antibodies specifically bind to human TIMP-1 with a K_d selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.5 M, about 0.6 nM, about 2 nM, about 7 nM, about 10 nM, about 11 nM, and about 13 nM.
- Other human antibodies of the invention specifically bind to rat TIMP-1 with a K_d of about 0.1 nM to about 10 μM, about 2 nM to about 1 μM, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 1.3 nM to about 13 nM, about 1.8 nM to about 10 nM, about 2 nM to about 9 nM, about 1.3 nM to about 9 nM, and about 2 nM to about 10 nM. Preferred K_d s range from about 0.8 nM, about 1 nM, about 1.3 nM, about 1.9 nM, about 2 nM, about 3 nM, about 9 nM, about 10 nM, about 13 nM, about 14 nM, and about 15 nM.
- [59] Preferably, antibodies of the invention neutralize an MMP-inhibiting activity of the TIMP-1. The MMP can be, for example, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-19, MMP-20 or MMP-23.
- [60] IC₅₀ for neutralizing MMP-inhibiting activity of TIMP-1 can be measured by any means known in the art. Preferably, IC₅₀ is determined using the high throughput fluorogenic assay described in Bickett *et al.*, *Anal. Biochem. 212*, 58-64, 1993. In a typical fluorogenic assay, the IC₅₀ of a human antibody for neutralizing human TIMP-1 MMP-inhibiting activity ranges from about .1 nM to about 200 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 0.2 nM to about 11 nM, about 0.2 nM to about 4 nM to about

11 nM. The IC₅₀ for neutralizing human TIMP-1 MMP-inhibiting activity of some human antibodies is about 0.2 nM, about 0.3 nM, about 0.4 nM, about 4 nM, about 7 nM, about 9 nM, and about 11 nM.

- [61] A typical IC₅₀ for neutralizing rat TIMP-1 MMP-inhibiting activity ranges from about .1 nM to about 300 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 1.1 nM to about 14 nM, about 1.6 nM to about 11 nM, about 3 nM to about 7 nM, about 1.1 nM to about 7 nM, about 1.1 nM to about 11 nM, about 3 nM to about 11 nM, and about 3 nM to about 14 nM. The IC₅₀ for neutralizing rat TIMP-1 MMP-inhibiting activity of some human antibodies is about 1.1 nM, about 1.6 nM, about 3 nM, about 7 nM, about 11 nM, about 14 nM, about 19 nM, about 20 nM, about 30 nM, and about 100 nM.
- [62] Preferred human antibodies of the invention are those for which the K_d for binding to TIMP-1 and the IC₅₀ for neutralizing the MMP-inhibiting activity of the TIMP-1 are approximately equal.
- [63] A number of human antibodies having the TIMP-1 binding and MMP-inhibiting activity neutralizing characteristics described above have been identified by screening the MorphoSys HuCAL® Fab 1 library. The CDR cassettes assembled for the HuCAL® library were designed to achieve a length distribution ranging from 5 to 28 amino acid residues, covering the stretch from position 95 to 102. Knappik et al., J. Mol. Biol. 296, 57-86, 2000. Some clones, however, had shorter VHCDR3 regions. In fact, it is a striking feature of anti-human TIMP-1 human antibodies identified from this library that they all exhibit the combination VH312 and a relatively short VHCDR3 region, typically four amino acids.
- [64] In some embodiments of the invention, the VHCDR3 region of a human antibody has an amino acid sequence shown in SEQ ID NOS:1-43. In other embodiments of the invention, the VLCDR3 region of a human antibody has an amino acid sequence shown in SEQ ID NOS:44-86. See Tables 2, 3, and 7. Human antibodies which have TIMP-1

binding and MMP-inhibiting activity neutralizing characteristics of antibodies such as those described above and in Tables 2, 3, and 7 also are human antibodies of the invention.

Obtaining human antibodies

- [65] Human antibodies with the TIMP-1 binding and MMP-activity neutralizing characteristics described above can be identified from the MorphoSys HuCAL® library as follows. Human or rat TIMP-1, for example, is coated on a microtiter plate and incubated with the MorphoSys HuCAL® Fab phage library (see Example 1, below). Those phage-linked Fabs not binding to TIMP-1 can be washed away from the plate, leaving only phage which tightly bind to TIMP-1. The bound phage can be eluted, for example, by a change in pH or by elution with *E. coli* and amplified by infection of *E. coli* hosts. This panning process can be repeated once or twice to enrich for a population of antibodies that tightly bind to TIMP-1. The Fabs from the enriched pool are then expressed, purified, and screened in an ELISA assay. The identified hits are then screened in the enzymatic assay described in Bickett *et al.*, 1993, and Bodden *et al.*, 1994. Those Fabs that lead to the degradation of the peptide are likely the ones which bind to TIMP-1, thereby blocking its interaction to MMP-1.
- The initial panning of the HuCAL® Fab 1 library also can be performed with TIMP-1 as [66] the antigen in round one, followed in round 2 by TIMP-1 peptides fused to carrier proteins, such as BSA or transferrin, and in round 3 by TIMP-1 again. Human TIMP-1 peptides which can be used for panning include human TIMP-1 residues 2-12 NO:88: ID NO:87; CTSVPPHPQTAF, SEO (TCVPPHPOTAF, SEQ STCVPPHPQTAF, SEQ ID NO:89; STSVPPHPQTAFC, SEQ ID NO:90), 28-36 (CEVNOTTLYO, SEO ID NO:91), 64-75 (PAMESVCGYFHR, SEQ ID NO:92), 64-79 (PAMESVCGYFHRSHNR, SEQ ID NO:93; CPAMESVSGYFHRSHNR, SEQ ID 145-157 PAMESVSGYFHRSHNRC, ID NO:95), and NO:94; SEQ (CLWTDQLLQGSE, SEQ ID NO:96). These peptide sequences are selected from

regions of human TIMP-1 that are predicted to interact with MMPs. See Gomis-Ruth et al., Nature 389, 77-81, 1997. Directing Fabs toward the MMP-interacting region of human TIMP-1 in round 2 should increase the chance of identifying Fabs that can block the ability of human TIMP-1 to inhibit human MMP-1 activity.

- [67] Another method that can be used to improve the likelihood of isolating neutralizing Fabs is the panning on human TIMP-1 and eluting the binding Fabs with human MMP-1. This strategy should yield higher affinity antibodies than would otherwise be obtained.
- [68] Details of the screening process are described in the specific examples, below. Other selection methods for highly active specific antibodies or antibody fragments can be envisioned by those skilled in the art and used to identify human TIMP-1 antibodies.
- [69] Human antibodies with the characteristics described above also can be purified from any cell that expresses the antibodies, including host cells that have been transfected with antibody-encoding expression constructs. The host cells are cultured under conditions whereby the human antibodies are expressed. A purified human antibody is separated from other compounds that normally associate with the antibody in the cell, such as certain proteins, carbohydrates, or lipids, using methods well known in the art. Such methods include, but are not limited to, size exclusion chromatography, ammonium sulfate fractionation, ion exchange chromatography, affinity chromatography, and preparative gel electrophoresis. A preparation of purified human antibodies is at least 80% pure; preferably, the preparations are 90%, 95%, or 99% pure. Purity of the preparations can be assessed by any means known in the art, such as SDS-polyacrylamide gel electrophoresis. A preparation of purified human antibodies of the invention can contain more than one type of human antibody with the TIMP-1 binding and neutralizing characteristics described above.
- [70] Alternatively, human antibodies can be produced using chemical methods to synthesize its amino acid sequence, such as by direct peptide synthesis using solid-phase techniques (Merrifield, J. Am. Chem. Soc. 85, 2149-54, 1963; Roberge et al., Science 269, 202-04,

1995). Protein synthesis can be performed using manual techniques or by automation. Automated synthesis can be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Optionally, fragments of human antibodies can be separately synthesized and combined using chemical methods to produce a full-length molecule.

[71] The newly synthesized molecules can be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, PROTEINS: STRUCTURES AND MOLECULAR PRINCIPLES, WH Freeman and Co., New York, N.Y., 1983). The composition of a synthetic polypeptide can be confirmed by amino acid analysis or sequencing (e.g., using Edman degradation).

Assessment of therapeutic utility of human antibodies

- To assess the ability of a particular antibody to be therapeutically useful to treat, liver fibrosis, for example, the antibody can be tested *in vivo* in a rat liver fibrosis model. Thus, preferred human antibodies of the invention are able to block both human and rat TIMP-1 activity. If desired, human Fab TIMP-1 antibodies can be converted into full immunoglobulins, for example IgG₁ antibodies, before therapeutic assessment. This conversion is described in Example 5, below.
- [73] To identify antibodies that cross-react with human and rat TIMP-1, an ELISA can be carried out using rat TIMP-1. Functional cross-reactivity can be confirmed in an enzymatic assay, as described in Bickett et al., Anal. Biochem. 212, 58-64, 1993. The assay uses human or rat TIMP-1, human MMP-1 or rat MMP-13 (the rat counterpart of human MMP-1), and a synthetic fluorogenic peptide substrate. Enzyme activity of uncomplexed MMP-1 (or MMP-13) is assessed by observing an increase in a fluorescence signal.
- [74] Antibodies that block human and/or rat TIMP-1 activity can be screened in an ELISA assay that detects the decrease of TIMP-1/MMP-1 complex formation in cultures of

HepG2 cells. Antibodies that meet this criteria can then be tested in a rat liver fibrosis model to assess therapeutic efficacy and correlate this efficacy with the ability of the antibodies to block TIMP-1 inhibition of MMP-1 in vitro.

[75] Antibodies that demonstrate therapeutic efficacy in the rat liver fibrosis model can then be tested for binding to and blockade of TIMP-2, -3, and -4 in an *in vitro* enzymatic assay. Blocking the minimum number of TIMPs necessary for efficacy in liver fibrosis or other TIMP-associated pathology is preferable to minimize potential side effects.

Polynucleotides encoding human TIMP-1 antibodies

- [76] The invention also provides polynucleotides encoding human TIMP-1 antibodies. These polynucleotides can be used, for example, to produce quantities of the antibodies for therapeutic or diagnostic use.
- [77] Polynucleotides that can be used to encode the VHCDR3 regions shown in SEQ ID NOS:1-43 are shown in SEQ ID NOS:226-268, respectively. Polynucleotides that can be used to encode the VLCDR3 region shown in SEQ ID NOS:44-86 are shown in SEQ ID NOS:183-225, respectively. Polynucleotides that encode heavy chains (SEQ ID NOS:140-182) and light chains (SEQ ID NOS:97-139) of human antibodies of the invention that have been isolated from the MorphoSys HuCAL® library are shown in SEQ ID NOS:269-311 and SEQ ID NOS:312-354, respectively.
- Polynucleotides of the invention present in a host cell can be isolated free of other cellular components such as membrane components, proteins, and lipids. Polynucleotides can be made by a cell and isolated using standard nucleic acid purification techniques, or synthesized using an amplification technique, such as the polymerase chain reaction (PCR), or by using an automatic synthesizer. Methods for isolating polynucleotides are routine and are known in the art. Any such technique for obtaining a polynucleotide can be used to obtain isolated polynucleotides encoding antibodies of the invention. For example, restriction enzymes and probes can be used to

isolate polynucleotides which encode the antibodies. Isolated polynucleotides are in preparations that are free or at least 70, 80, or 90% free of other molecules.

- [79] Human antibody-encoding DNA molecules of the invention can be made with standard molecular biology techniques, using mRNA as a template. Thereafter, DNA molecules can be replicated using molecular biology techniques known in the art and disclosed in manuals such as Sambrook et al. (1989). An amplification technique, such as PCR, can be used to obtain additional copies of the polynucleotides.
- [80] Alternatively, synthetic chemistry techniques can be used to synthesize polynucleotides encoding antibodies of the invention. The degeneracy of the genetic code allows alternate nucleotide sequences to be synthesized that will encode an antibody having, for example, one of the VHCDR3, VLCDR3, light chain, or heavy chain amino acid sequences shown in SEQ ID NOS:1-43, 44-86, 97-139, or 140-182, respectively.

Expression of polynucleotides

- [81] To express a polynucleotide encoding a human antibody of the invention, the polynucleotide can be inserted into an expression vector that contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods that are well known to those skilled in the art can be used to construct expression vectors containing sequences encoding human antibodies and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook *et al.* (1989) and in Ausubel *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, N.Y., 1995. See also Examples 1-3, below.
- [82] A variety of expression vector/host systems can be utilized to contain and express sequences encoding a human antibody of the invention. These include, but are not limited to, microorganisms, such as bacteria transformed with recombinant

bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors, insect cell systems infected with virus expression vectors (e.g., baculovirus), plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids), or animal cell systems.

- [83] The control elements or regulatory sequences are those non-translated regions of the vector -- enhancers, promoters, 5' and 3' untranslated regions -- which interact with host cellular proteins to carry out transcription and translation. Such elements can vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, can be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the BLUESCRIPT phagemid (Stratagene, LaJolla, Calif.) or pSPORT1 plasmid (Life Technologies) and the like can be used. The baculovirus polyhedrin promoter can be used in insect cells. Promoters or enhancers derived from the genomes of plant cells (e.g., heat shock, RUBISCO, and storage protein genes) or from plant viruses (e.g., viral promoters or leader sequences) can be cloned into the vector. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are preferable. If it is necessary to generate a cell line that contains multiple copies of a nucleotide sequence encoding a human antibody, vectors based on SV40 or EBV can be used with an appropriate selectable marker.
- [84] Large scale production of human TIMP-1 antibodies can be carried out using methods such as those described in Wurm et al., Ann. N.Y. Acad. Sci. 782, 70-78, 1996, and Kim et al., Biotechnol. Bioengineer. 58, 73-84, 1998.

Pharmaceutical compositions

[85] Any of the human TIMP-1 antibodies described above can be provided in a pharmaceutical composition comprising a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier preferably is non-pyrogenic. The compositions can

be administered alone or in combination with at least one other agent, such as stabilizing compound, which can be administered in any sterile, biocompatible pharmaceutical carrier, including, but not limited to, saline, buffered saline, dextrose, and water. A variety of aqueous carriers may be employed, e.g., 0.4% saline, 0.3% glycine, and the like. These solutions are sterile and generally free of particulate matter. These solutions may be sterilized by conventional, well known sterilization techniques (e.g., filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, etc. The concentration of the antibody of the invention in such pharmaceutical formulation can vary widely, i.e., from less than about 0.5%, usually at or at least about 1% to as much as 15 or 20% by weight and will be selected primarily based on fluid volumes, viscosities, etc., according to the particular mode of administration selected. See U.S. Patent 5,851,525. If desired, more than one type of human antibody, for example with different K_d for TIMP-1 binding or with different IC₅₀s for MMP-inhibiting activity neutralization, can be included in a pharmaceutical composition.

- [86] The compositions can be administered to a patient alone, or in combination with other agents, drugs or hormones. In addition to the active ingredients, these pharmaceutical compositions can contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations which can be used pharmaceutically. Pharmaceutical compositions of the invention can be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, parenteral, topical, sublingual, or rectal means.
- [87] After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. Such labeling would include amount, frequency, and method of administration.

Methods of decreasing MMP-inhibiting activity of human TIMP-1

[88] The invention provides methods of decreasing an MMP-inhibiting activity of human or rat TIMP-1. Such methods can be used therapeutically, as described below, or in a research setting. Thus, the methods can be carried out in a cell-free system, in a cell culture system, or *in vivo*. *In vivo* methods of decreasing MMP-inhibiting activity of human or rat TIMP-1 are described below.

[89] Human TIMP-1 is contacted with a human antibody that binds to the human TIMP-1, thereby decreasing the MMP-inhibiting activity of the human TIMP-1 relative to human TIMP-1 activity in the absence of the antibody. The antibody can be added directly to the cell-free system, cell culture system, or to an animal subject or patient, or can be provided by means of an expression vector encoding the antibody.

Diagnostic methods

- The invention also provides diagnostic methods, with which human or rat TIMP-1 can be detected in a test preparation, including without limitation a sample of serum, lung, liver, heart, kidney, colon, a cell culture system, or a cell-free system (e.g., a tissue homogenate). Such diagnostic methods can be used, for example, to diagnose disorders in which TIMP-1 is elevated. Such disorders include, but are not limited to, liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute cardiac syndrome, lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, lung cancer, colon cancer, and idiopathic pulmonary fibrosis. When used for diagnosis, detection of an amount of the antibody-TIMP-1 complex in a test sample from a patient which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.
- [91] The test preparation is contacted with a human antibody of the invention, and the test preparation is then assayed for the presence of an antibody-TIMP-1 complex. If desired, the human antibody can comprise a detectable label, such as a fluorescent, radioisotopic,

chemiluminescent, or enzymatic label, such as horseradish peroxidase, alkaline phosphatase, or luciferase.

Optionally, the antibody can be bound to a solid support, which can accommodate automation of the assay. Suitable solid supports include, but are not limited to, glass or plastic slides, tissue culture plates, microtiter wells, tubes, silicon chips, or particles such as beads (including, but not limited to, latex, polystyrene, or glass beads). Any method known in the art can be used to attach the antibody to the solid support, including use of covalent and non-covalent linkages, passive absorption, or pairs of binding moieties attached to the antibody and the solid support. Binding of TIMP-1 and the antibody can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and microcentrifuge tubes.

Therapeutic methods

- [93] The invention also provides methods of ameliorating symptoms of a disorder in which TIMP-1 is elevated. These disorders include, without limitation, liver fibrosis alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, colon cancer, and scarring. See, e.g., Inokubo et al., Am. Heart J. 141, 211-17, 2001; Ylisirnio et al., Anticancer Res. 20, 1311-16, 2000; Holten-Andersen et al., Clin. Cancer Res. 6, 4292-99, 2000; Holten-Andersen et al., Br. J. Cancer 80, 495-503, 1999; Peterson et al., Cardiovascular Res. 46, 307-15, 2000; Arthur et al., Alcoholism: Clinical and Experimental Res. 23, 840-43, 1999; Iredale et al., Hepatol. 24, 176-84, 1996.
- [94] Human antibodies of the invention are particularly useful for treating liver fibrosis. All chronic liver diseases cause the development of fibrosis in the liver. Fibrosis is a programmed uniform wound healing response. Toxic damage or injury caused by foreign proteins cause the deposition of extracellular matrix such as collagen, fibronectin, and laminin. Liver fibrosis and cirrhosis can be caused by chronic degenerative diseases

of the liver such as viral hepatitis, alcohol hepatitis, autoimmune hepatitis, primary biliary cirrhosis, cystic fibrosis, hemochromatosis, Wilson's disease, and non-alcoholic steato-hepatitis, as well as chemical damage.

- [95] Altered degradation and synthesis of extracellular matrix (particularly collagens) play central roles in pathogenesis of liver fibrosis. In the early phases, hepatic stellate cells (HSC) are initially activated and release matrix metalloproteases with the ability to degrade the normal liver matrix. When HSC are fully activated, there is a net down-regulation of matrix degradation mediated by increased synthesis and extracellular release of tissue inhibitors of metalloprotease (TIMP)-1 and -2. The dynamic regulation of activity of metalloproteases during liver fibrosis makes them and their inhibitors targets for therapeutic intervention.
- Human antibodies of the invention are also particularly useful for treating lung fibrosis. Lung airway fibrosis is a hallmark of airway remodeling in patients with chronic asthma, so human antibodies of the invention are also particularly useful for chronic asthma. Airway remodeling is a well-recognized feature in patients with chronic asthma. TIMP-1 but not TIMP-2 levels were significantly higher in untreated asthmatic subjects than in glucocorticoid-treated subjects or controls (p < 0.0001), and were far greater than those of MMP-1, MMP-2, MMP-3, and MMP-9 combined (Mautino *et al.*, Am J Respir Crit Care Med 1999 160:324-330). TIMP-1 mRNA and protein expression are selectively and markedly increased in a murine model of bleomycin-induced pulmonary fibrosis (Am. J. Respir. Cell Mol. Biol. 24:599-607, 2001). This specific elevation of TIMP-1 without increase in MMPs in asthma patients suggests that inhibition of TIMP-1 by an antibody can restore normal collagen degradation in the lung.
- [97] Human antibodies of the invention are also particularly useful for treating cancer. TIMP-1 protein has been found to be elevated in plasma of colon (Holten-Andersen et al., Br J Cancer 1999, 80:495-503) and prostate (Jung et al., Int J Cancer, 1997, 74:220-223) cancer patients, and high TIMP-1 plasma level correlates with poor clinical outcome of

colon cancer (Holten-Andersen et al., Clin Cancer Res 2000 6:4292-4299). TIMP-1 induces dose-dependent proliferation of breast tumorigenic clonal cell line and tyrosine phosphorylation (Luparello et al, Breast Cancer Res Treat, 1999, 54:235-244). Therefore, the use of antibody against TIMP-1 may block its ability to induce cancer.

- [98] Human TIMP-1 antibodies can be used to prevent or diminish scar formation, such as scar formation after surgery (particularly ophthalmic surgery) or injury (such as a burn, scrape, crush, cut or tear injury).
- [99] In one embodiment of the invention, a therapeutically effective dose of a human antibody of the invention is administered to a patient having a disorder in which TIMP-1 is elevated, such as those disorders described above. Symptoms of the disorder, including deposition of extracellular matrix, as well as loss of tissue or organ function, are thereby ameliorated.

Determination of a Therapeutically Effective Dose

- [100] The determination of a therapeutically effective dose is well within the capability of those skilled in the art. A therapeutically effective dose refers to that amount of human antibody that reduces MMP-inhibiting activity of the TIMP-1 relative to the activity which occurs in the absence of the therapeutically effective dose.
- [101] The therapeutically effective dose can be estimated initially either in cell culture assays or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model also can be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. A rat liver fibrosis model is described in Example 6.
- [102] Therapeutic efficacy and toxicity, e.g., ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population) of a human antibody, can be determined by standard pharmaceutical procedures in cell cultures or experimental

animals. The dose ratio of toxic to the rapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50} .

- [103] Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.
- [104] The exact dosage will be determined by the practitioner, in light of factors related to the patient who requires treatment. Dosage and administration are adjusted to provide sufficient levels of the human antibody or to maintain the desired effect. Factors that can be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions can be administered every 3 to 4 days, every week, or once every two weeks depending on the half-life and clearance rate of the particular formulation.
- [105] Polynucleotides encoding human antibodies of the invention can be constructed and introduced into a cell either ex vivo or in vivo using well-established techniques including, but not limited to, transferrin-polycation-mediated DNA transfer, transfection with naked or encapsulated nucleic acids, liposome-mediated cellular fusion, intracellular transportation of DNA-coated latex beads, protoplast fusion, viral infection, electroporation, "gene gun," and DEAE- or calcium phosphate-mediated transfection.
- [106] Effective in vivo dosages of an antibody are in the range of about 5 mg to about 50 mg/kg, about 50 mg to about 5 mg/kg, about 100 mg to about 500 mg/kg of patient body weight, and about 200 to about 250 mg/kg of patient body weight. For administration of polynucleotides encoding the antibodies, effective in vivo dosages are in the range of

about 100 ng to about 200 ng, 500 ng to about 50 mg, about 1 mg to about 2 mg, about 5 mg to about 500 mg, and about 20 mg to about 100 mg of DNA.

- [107] The mode of administration of human antibody-containing pharmaceutical compositions of the invention can be any suitable route which delivers the antibody to the host. Pharmaceutical compositions of the invention are particularly useful for parenteral administration, *i.e.*, subcutaneous, intramuscular, intravenous, or intranasal administration.
- [108] All patents, patent applications, and references cited in this disclosure are expressly incorporated herein by reference. The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific examples, which are provided for purposes of illustration only and are not intended to limit the scope of the invention.

EXAMPLE 1

Construction of a Human Combinatorial Antibody Library (HuCAL® Fab 1)

- [109] Cloning of HuCAL® Fab 1. HuCAL® Fab 1 is a fully synthetic, modular human antibody library in the Fab antibody fragment format. HuCAL® Fab 1 was assembled starting from an antibody library in the single-chain format (HuCAL® -scFv; Knappik et al., J. Mol. Biol. 296, 55, 2000). HuCAL® Fab 1 was cloned into a phagemid expression vector pMORPH® 18 Fab1 (FIG. 3). This vector comprises the Fd fragment with a phoA signal sequence fused at the C-terminus to a truncated gene III protein of filamentous phage, and further comprises the light chain VL-CL with an ompA signal sequence. Both chains are under the control of the lac operon. The constant domains C?, C?, and CH are synthetic genes fully compatible with the modular system of HuCAL® (Knappik et al., 2000).
- [110] First, the V? and V? libraries were isolated from HuCAL®-scFv. V?l fragments were amplified by 15 PCR cycles (Pwo polymerase) with primers 5'-

GTGGTGCTCCGATATC-3' (SEQ ID NO:380) and 5'- AGCGTCACA-CTCGGTGCGGCTGGCCAAGAACGGTTA-3' (SEQ ID NO:381). PCR-products were digested with EcoRV / DraIII and gel-purified. VL?-chains were obtained by restriction digest with EcoRV / BsiWI and gel-purified. These V? and V? libraries were cloned into pMORPH® 18 Fab1 cut with EcoRV / DraIII and EcoRV / BsiWI, respectively. After ligation and transformation in E. coli TG-1, library sizes of 4.14 x 10⁸ and 1.6 x 10⁸, respectively, were obtained, in both cases exceeding the V? diversity of HuCAL®-scFv.

- [111] Similarly, the VH library was isolated from HuCAL®-scFv by restriction digest using Styl / MunI. This VH library was cloned into the pMORPH® 18-V? and V? libraries cut with Styl / MunI. After ligation and transformation in E. coli TG-1, a total library size of 2.09 x 10¹⁰ was obtained, with 67% correct clones (as identified by sequencing of 207 clones).
- [112] Phagemid rescue, phage amplification and purification. HuCAL® Fab was amplified in 2 x TY medium containing 34 μg/ml chloramphenicol and 1 % glucose (2 x TY-CG). After helper phage infection (VCSM13) at 37°C at an OD600 of about 0.5, centrifugation and resuspension in 2 x TY / 34 μg/ml chloramphenicol/ 50 μg/ml kanamycin, cells were grown overnight at 30°C. Phage were PEG-precipitated from the supernatant (Ausubel et al., 1998), resuspended in PBS/20% glycerol, and stored at -80°C. Phage amplification between two panning rounds was conducted as follows: mid-log phase TG1-cells were infected with eluted phage and plated onto LB-agar supplemented with 1% of glucose and 34 μg/ml of chloramphenicol. After overnight incubation at 30°C, colonies were scraped off and adjusted to an OD600 of 0.5. Helper phage were added as described above.

EXAMPLE 2

Solid phase panning

[113] Wells of MaxiSorpTM microtiter plates (Nunc) were coated with rat- or human TIMP protein diluted to 50 μg/ml dissolved in PBS (2 μg/well). After blocking with 5% non-fat dried milk in PBS, 1–5 x 10¹² HuCAL[®] Fab phage purified as above were added for 1h at 20°C. After several washing steps, bound phage were eluted by pH-elution with 100 mM triethylamine and subsequent neutralization with 1M TRIS-Cl pH 7.0. See Krebs *et al.*, *J. Immunol. Meth. 254*, 67, 2001. Two to three rounds of panning were performed with phage amplification conducted between each round as described above.

EXAMPLE 3

Solution panning

[114] Biotinylated antigen was diluted to 40 nM in PBS, 1013 HuCAL®-Fab 1 phage were added and incubated for 1 h at 20°C. Phage-antigen complexes were captured on Neutravidin plates (Pierce). After several washing steps, bound phages were eluted by different methods (Krebs et al., 2001). Two rounds of panning were routinely performed.

EXAMPLE 4

Subcloning of selected Fab fragments for expression

[115] The Fab-encoding inserts of the selected HuCAL® Fab 1 fragments were subcloned into the expression vector pMORPH® x7_FS (Knappik et al., J. Mol. Biol. 296, 55, 2000) to facilitate rapid expression of soluble Fab. The DNA preparation of the selected HuCAL® Fab 1 clones was digested with XbaI / EcoRI, thus cutting out the Fab encoding insert (ompA-VL and phoA-Fd). Subcloning of the purified inserts into the XbaI / EcoRI cut vector pMORPH® x7, previously carrying a scFv insert, produces a Fab expression vector designated pMORPH® x9_Fab1_FS (FIG. 4). Fabs expressed in this vector carry two C-terminal tags (FLAGTM and Strep-tagII) for detection and purification.

EXAMPLE 5

Identification of TIMP-binding Fab fragments by ELISA

[116] The wells of 384-well Maxisorp ELISA plates were coated with 20 μl/well solutions of rat TIMP or human TIMP at a concentration of 5 μg/ml diluted in coating buffer. Expression of individual Fab in *E. coli* TG-1 from expression vector pMORPH[®] x9_FS was induced with 0.5 mM IPTG for 12 h at 30°C. Soluble Fab was extracted from the periplasm by osmotic shock (Ausubel *et al.*, 1998) and used in an ELISA. The Fab fragment was detected after incubation with alkaline phosphatase-conjugated anti-Fab antibody (Dianova), followed by development with Attophos substrate (Roche) and measurement at Ex450 nm / Em535 nm. Values at 370 nm were read out after addition of horseradish peroxidase-conjugated anti-mouse IgG antibody and POD soluble substrate (Roche Diagnostics).

EXAMPLE 6

Expression and purification of HuCAL®-Fab 1 antibodies in E. coli

[117] Expression of Fab fragments encoded by pMORPH® x9_FS in TG-1 cells was carried out in shaker flask cultures with 1 liter of 2xTY medium supplemented with 34 µg/ml chloramphenicol. After induction with 0.5 mM IPTG, cells were grown at 22°C for 16 h. Periplasmic extracts of cell pellets were prepared, and Fab fragments were isolated by Strep-tactin® chromatography (IBA, Goettingen, Germany). The apparent molecular weights were determined by size exclusion chromatography (SEC) with calibration standards. Concentrations were determined by UV-spectrophotometry.

EXAMPLE 7

Construction of HuCAL® immunoglobulin expression vectors

[118] Heavy chain cloning. The multiple cloning site of pcDNA3.1+ (Invitrogen) was removed (NheI / ApaI), and a stuffer compatible with the restriction sites used for HuCAL® design

was inserted for the ligation of the leader sequences (*NheI | EcoRI*), VH-domains (*EcoRI | BlpI*), and the immunoglobulin constant regions (*BlpI | ApaI*). The leader sequence (EMBL M83133) was equipped with a Kozak sequence (Kozak, 1987). The constant regions of human IgG₁ (PIR J00228), IgG₄ (EMBL K01316), and serum IgA₁ (EMBL J00220) were dissected into overlapping oligonucleotides with lengths of about 70 bases. Silent mutations were introduced to remove restriction sites non-compatible with the HuCAL[®] design. The oligonucleotides were spliced by overlap extension-PCR.

- [119] Light chain cloning. The multiple cloning site of pcDNA3.1/Zeo+ (Invitrogen) was replaced by two different stuffers. The ?-stuffer provided restriction sites for insertion of a ?-leader (NheI / EcoRV), HuCAL®-scFv V?-domains (EcoRV / BsiWI,) and the ?-chain constant region (BsiWI / ApaI). The corresponding restriction sites in the ?-stuffer were NheI / EcoRV (?-leader), EcoRV / HpaI (V?- domains), and HpaI / ApaI (?-chain constant region). The ?-leader (EMBL Z00022) as well as the ?-leader (EMBL L27692) were both equipped with Kozak sequences. The constant regions of the human ?- (EMBL J00241) and ?-chain (EMBL M18645) were assembled by overlap extension-PCR as described above.
- [120] Generation of IgG-expressing CHO-cells. CHO-K1 cells were co-transfected with an equimolar mixture of IgG heavy and light chain expression vectors. Double-resistant transfectants were selected with 600 μg/ml G418 and 300 μg/ml Zeocin (Invitrogen) followed by limiting dilution. The supernatant of single clones was assessed for IgG expression by capture-ELISA (see below). Positive clones were expanded in RPMI-1640 medium supplemented with 10% ultra-low IgG-FCS (Life Technologies). After adjusting the pH of the supernatant to 8.0 and sterile filtration, the solution was subjected to standard protein A column chromatography (Poros 20 A, PE Biosystems).

EXAMPLE 8

Design of the CDR3 libraries

- [121] V? positions 1 and 2. The original HuCAL® master genes were constructed with their authentic N-termini: V?11: QS (CAGAGC), V?12: QS (CAGAGC), and V?13: SY (AGCTAT). Sequences containing these amino acids are shown in WO 97/08320. During HuCAL® library construction, the first two amino acids were changed to DI to facilitate library cloning (EcoRI site). All HuCAL® libraries contain V?1 genes with the EcoRV site GATATC (DI) at the 5'-end. All HuCAL® kappa genes (master genes and all genes in the library) contain DI at the 5'-end.
- [122] VH position 1. The original HuCAL® master genes were constructed with their authentic N-termini: VH1A, VH1B, VH2, VH4, and VH6 with Q (=CAG) as the first amino acid and VH3 and VH5 with E (=GAA) as the first amino acid. Sequences containing these amino acids are shown in WO 97/08320. In the HuCAL® Fab 1 library, all VH chains contain Q (=CAG) at the first position.
- [123] V?1/V?3 position 85. Because of the cassette mutagenesis procedure used to introduce the CDR3 library (Knappik et al., J. Mol. Biol. 296, 57-86, 2000), position 85 of V?1 and V?3 can be either T or V. Thus, during HuCAL® scFv 1 library construction, position 85 of V?1 and V?3 was varied as follows: V?1 original, 85T (codon ACC); V?1 library, 85T or 85V (TRIM codons ACT or GTT); V?3 original, 85V (codon GTG); V?3 library, 85T or 85V (TRIM codons ACT or GTT); the same applies to HuCAL® Fab1.
- [124] CDR3 design. All CDR3 residues which were kept constant are indicated in FIG. 1.
- [125] CDR3 length. The designed CDR3 length distribution is as follows. Residues which were varied are shown in brackets (x) in FIG. 1. V kappa CDR3, 8 amino acid residues (position 89 to 96) (occasionally 7 residues), with Q90 fixed; V lambda CDR3, 8 to 10 amino acid residues (position 89 to 96) (occasionally 7-10 residues), with Q89, S90, and

D92 fixed; and VH CDR3, 5 to 28 amino acid residues (position 95 to 102) (occasionally 4-28), with D101 fixed.

EXAMPLE 9

Chronic carbon tetrachloride-induced liver fibrosis

- [126] Sprague Dawley rats (200-220 g) are used in an *in vivo* model of liver fibrosis. To maximally induce microsomal metabolism of carbon tetrachloride metabolism, animals receive 1 g/l isoniazid with their drinking water starting one week before the administration of carbon tetrachloride. Carbon tetrachloride (1:1 in mineral oil) is administered orally every fifth day at a dose of 0.2 ml/100 g body weight. A human TIMP-1 antibody is administered intravenously, either once or repeatedly, during the period of carbon tetrachloride treatment. Necropsy is performed after 5-7 weeks of treatment. McLean *et al.*, *Br. J. Exp. Pathol.* 50, 502-06, 1969.
- [127] Transverse cylinders of liver tissue are cut from the right liver lobe, fixed in formaldehyde, and embedded in paraffin. The amount of fibrosis in the liver is indicated by the picrosirius red-stained fibrotic areas. Picrosirius-positive areas are determined in several centrilobular fields in each section. Parameters of color detection are standardized and kept constant throughout the experiment. The field are selected using a standardized grid which covers an area of 31 mm2. A Leica Quantimed 500 MC system is used for morphometry.

EXAMPLE 10

Hydroxyproline determination

[128] The method of Prockop & Udenfried, Anal. Biochem. 1, 228-39, 1960, can be used to determine hydroxyproline is liver tissues, with the following modifications. Liver specimens of 60-90 mg wet weight are dried and hydrolyzed in 6 N HCl at 100 °C for 17 h. The hydrolyzed material is dried and reconstituted in 5 ml of deionized water. Two

hundred microliters of this hydrolysate are mixed with 200 ml of ethanol and 200 ml chloramin T solution (0.7 % in citrate buffer [5.7 g sodium acetate, 3.75 g trisodium citrate, 0.55 g citric acid, 38.5 ml ethanol, made up to 100 ml with water]) and allowed to oxidize for 20 min at room temperature. Four hundred microliters of Ehrlich's reagent (12 g p-dimethylaminobenzldehyde in 40 ml ethanol and 2.7 ml H₂SO₄) are added. After incubation for 3 h at 35 °C, absorbance at 573 nm is measured.

EXAMPLE 11

Affinity determination by surface plasmon resonance measurements (BIAcoreTM)

[129] For affinity determination, monomeric fractions of affinity and SEC purified Fab fragments or purified IgG1 molecules were used. All experiments were conducted in HBS buffer at a flow rate of 20 μl/min at 25°C on a BIAcoreTM instrument. Antigens in 100 mM sodium acetate pH 5.0 were coupled to a CM 5 sensor chip using standard EDC-NHS coupling chemistry. Applying 3-4 μl of 5 μg/ml TIMP-1 typically resulted in 500 resonance units for kinetic measurements. All sensograms were fitted globally using BIA evaluation software. For monovalent Fab fragments a monovalent fit (Langmuir binding) and for IgGs a bivalent fit was applied.

EXAMPLE 12

IC50 determination in human TIMP-1/human MMP-1 and rat TIMP-1/rat MMP-13 assay

[130] Purified Fab fragments or IgGs were used for IC₅₀ determination. Antibodies were diluted in triplicate to the indicated concentrations in assay buffer containing 0.05% BSA. After addition of TIMP (final conc. 1.2 nM or 0.4 nM for modified in human TIMP-1/human MMP-1 assay), MMP (final conc. 1.2 nM or 0.4 nM for modified in human TIMP-1/human MMP-1 assay), and peptide substrate (final conc. 50 μM) and incubation for 1-3 h at 37°C, fluorescence at Ex320 nm/Em430 nm was measured.

[131] The following controls were included in the assay and used as reference values for IC₅₀ determination:

- A: MMP + substrate: this value was defined as 100% MMP activity in absence of antibody and TIMP.
- B: MMP + TIMP + substrate: this value was defined as maximum inhibition achieved in the assay and calculated as a % of total MMP activity.
- [132] To define the concentration of antibody that resulted in 50% reversal of inhibition (IC₅₀), the following procedure was used:
 - The value for 50% reversal of inhibition (expressed as % activity MMP) was calculated as: Y = [(A B)/2] + B.
 - MMP activity was plotted against concentration of antibody in the assay.
 - The concentration of antibody that results in 50% reversal of inhibition (Y) was read on the x-axis and defined as IC₅₀.
 - Error bars in the graphs were derived from triplicate wells in one assay.
 - Standard deviations for IC₅₀ values were calculated from 3 independent assays.

EXAMPLE 13

Affinity maturation of selected Fab by stepwise exchange of CDR cassettes

[133] To increase affinity and biological activity of selected antibody fragments, CDR regions were optimized by cassette mutagenesis using trinucleotide directed mutagenesis (Virnekäs et al., 1994). Fab fragments in expression vector pMORPH® x9 were cloned into phagemid vector pMORPH®_18 using EcoRI / XbaI restriction sites. CDR cassettes containing several diversified positions were synthesized and cloned into Fab fragments in pMORPH® 18 using unique restriction sites (Knappik et al., 2000). Affinity

maturation libraries were generated by transformation into $E.\ coli$ TOP10F, and phage were prepared as described above. Phage displaying Fab fragments with improved affinity were selected by 2-3 rounds solution panning using stringent washing conditions (e.g., competition with 1 μ M non-biotinylated antigen or washing for up to 48 h with frequent buffer exchange) and limited amounts of antigen (0.04 – 4 nM). Seventeen human TIMP-1 antibodies were tested for affinity to human TIMP-1 (with some tested for affinity to rat TIMP-1) using a BIAcoreTM assay. The K_d of these antibodies for human TIMP-1 and rat TIMP-1 are shown in Table 1.

Table 1. Overview of species cross-reactive Fab

·					
IC ₅₀ in rat protease assay	Mn 008 <	Non blocking	Mu5 -/+ 79	Mn 300 <	> 100 nM
IC ₅₀ in human protease assay	115 +/- 15 nM		> 300 nM	~11 nM	> 100 nM
Monovalent K _D rat TIMP-1	4517 +/- 2400 nM	~ 3200 nM	36 +/- 2 nM	Mn 535∽	~108 nM
Monovalent K _D human TIMP-1	25+/- 16 nM*	~74 nM	S20+/- 20 nM	Мп €~	~7500 nM
Fab	MS-BW-25	MS-BW-27	MS-BW-21	MS-BW-38	MS-BW-39

* In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

~ Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 14

Screening for Fab with improved off-rates by koff ranking using surface plasmon resonance

- Phage eluted after solution panning were used to infect *E. coli* TG-1 and plated on agar plates containing 34 μg/ml chloramphenicol. Clones were picked into 96 well plates and used to produce Fab fragments. On the same plate, parental clones were inoculated as controls. Soluble Fab was extracted from the periplasm by osmotic shock (Ausubel *et al.*, 1998) and used for koff ranking in BIAcoreTM.
- [135] All measurements were conducted in HBS buffer at a flow rate of 20 μl/min at 25°C on a BIAcoreTM instrument. Antigens in 100 mM sodium acetate pH 4.5 were coupled to a CM 5 sensor chip using standard EDC-NHS coupling chemistry. Applying 10 μl of 25 μg/ml TIMP-1 typically resulted in 5000 resonance units for koff ranking. All sensograms were fitted using BIA evaluation software. Clones with improved off rate were selected by comparison to parental clones.

EXAMPLE 15

Generation of species cross-reactive antibodies

[136] To maximize the likelihood of obtaining blocking antibodies that are cross-reactive between human and rat TIMP-1, alternating pannings were carried out on rat and human protein. Additionally, all antibodies selected by pannings on solely the human or rat TIMP-1 protein were analyzed for cross-reactivity in order to check for cross-reactive antibodies that might be selected by chance. Antibodies selected from these pannings were analyzed for cross-reactivity in ELISA using crude *E. coli* extracts. Cross-reactive antibodies in this assay were subjected to expression in 1-liter scale followed by purification. Purified antibodies were tested for cross-reactivity in BIAcore™ and protease assays (Table 1).

[137] As shown in Table 1, a total of five different Fab cross-reactive with human and rat TIMP-1 were generated. BIAcoreTM measurements revealed that although these antibodies clearly bind to human and rat TIMP-1, affinities for both species differ by at least a factor of 50. An antibody used for human therapy or in an animal model should have an affinity to the target protein in the low nanomolar, preferably in the subnanomolar range. As none of the above-described antibodies had affinities in this range for both species, these antibodies were not considered useful for further experiments or development.

EXAMPLE 16

Generation of blocking antibodies against human TIMP-1

- [138] To generate blocking antibodies against human TIMP-1, the HuCAL®-Fab 1 library was used for antibody selection (AutoPan®) on purified TIMP-1 protein followed by subcloning and expression of the selected Fab fragments in *E. coli*. Crude antibody-containing *E. coli* extracts were used for primary antibody characterization in ELISA (AutoScreen®). Purified Fab proteins were subjected to further characterization in ELISA, TIMP-1/MMP-1 assay and BIAcore™. A total of 6100 clones were analyzed in AutoScreen®, 670 of them showed binding to human TIMP-1. Sequence analysis revealed that in total seven unique antibody clones had been selected (Table 2). For these seven Fab clones, the affinities measured in BIAcore™ were in the range of 10 − 180 nM (Table 4). When tested in the human protease assay, five of them were able to block the interaction between human TIMP-1 and MMP-1. The concentration of monovalent Fab needed to reverse the inhibitory effect of human TIMP-1 on human MMP-1 activity by 50% (IC₅₀) was in the range of 11 100 nM (Table 2). The most active Fab clones are MS-BW-3 (K_d 13 nM; IC₅₀ 11 nM) and MS-BW-28 (K_d 10 nM; IC₅₀ 22 nM).
- [139] A striking feature of antibodies selected against human TIMP-1 is that they all exhibit the combination VH312 and a relatively short VH-CDR3 region, predominantly four amino acids (see Table 2). The HCDR3 cassettes assembled for the HuCAL®-Fab 1 library

were designed to achieve a length distribution ranging from 5 to 28 amino acid residues. A four amino acid HCDR3 can occur in the library due to TRIM deletion, but is considered a very rare event. Another remarkable feature was the high degree of sequence homology among the selected LCDR3 sequences.

Table 2. Overview of anti-human TIMP-1 Fab

46		Framewo	rk + CD	Framework + CDR 3 sequence	Monovalent K _D	IC ₅₀ in human protease
ag.	ΑМ	HCDR3	٦۸	LCDR3	to human TIMP-1	assay
MS-BW-1	H3	FMDI, SEQ ID NO:1	72	72 QSYDYQQFT, SEQ ID NO:44	65+/-13 nM*	>100 nM
MS-BW-2	铝	GFDY, SEQ ID NO:2	72	QSYDFKTYL, SEQ ID NO:45	180+/-28 nM	>100 nM
MS-BW-3	H3	FLDI, SEQ ID NO:3	32	QSYDFLRFS, SEQ ID NO:46	13+/-2 nM	11+/-2nM
MS-BW-25	H3	TFPIDADS, SEQ ID NO:4	12	QSYDFINVI, SEQ ID NO:47	25+/-16nM	115+/-15 nM
MS-BW-26	H3	GHVDY, SEQ ID NO:5	32	QSYDFVRFM, SEQ ID NO:48	~100 nM	non blocking
MS-BW-27	H3	YWRGLSFDI, SEQ ID NO:6	7.5	QSYDFYKEN, SEQ ID NO:49	~74	non blocking
MS-BW-28	H3	FFDY, SEQ ID NO:7	.72	QSYDFRRFS, SEQ ID NO:50	10+/-1 nM	22+/-2nM

In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

Indicates preliminary data, in cases where measurement was done only once.

?

EXAMPLE 17

Increasing the affinity of selected anti-human TIMP-1 antibodies

[140] In order to increase the affinity of monovalent anti-human TIMP-1 Fab fragments to the sub-nanomolar range, a step-wise affinity maturation approach was applied, by optimizing CDR sequences and keeping framework regions constant.

Affinity maturation by light chain cloning

- [141] The CDR3 sequences of the two antibody fragments with highest affinity (MS-BW-3 and MS-BW-28) had the remarkable feature of an unusually short four amino acid HCDR3 sequence. Furthermore, each Fab had a very similar LCDR3 sequence. This indicates that MS-BW-3 and MS-BW-28 bind to the same epitope and that this epitope might tolerate only a very small subset of CDR3 sequences. As a four amino acid HCDR3 is a very rare event in the library, it can be anticipated that in the initial library not all possible combinations of the short HCDR3 and the preferred LCDR3 are present. Therefore, it was considered that another combination of the selected HCDR3 and LCDR3 sequences might increase the affinity. For this approach, the heavy chain of MS-BW-3 and MS-BW-28 were paired with the light chains of MS-BW-1, -2, -3, -25, -26, -27, and -28 by cloning.
- [142] The resulting constructs were transformed into *E. coli* and expressions/purifications in 1-liter scale were performed. Of the 12 new constructs, 10 resulted in functional Fab molecules. These were analyzed in BIAcoreTM and human protease assay as summarized in Table 3. The best antibody named MS-BW-44 had a monovalent affinity of 2 nM and an IC50 of 4 nM (FIG. 7) and was thus improved by a factor of 6.5 (K_d) or 2.75 (IC₅₀).

Table 3. Overview of Fab derived from light chain clouing

Ġ	Framew	Framework + CDR 3 sequence			Monovalent K _D to	IC ₅₀ * in human
ran	νн	HCDR3	VL	LCDR3	human TIMP-1	protease assay
MS-BW-40	H3	FLDI, SEQ ID NO:3	12	QSYDYQQFT, SEQ ID NO:44	—49 nM	> 100 nM
MS-BW-41	Н3	FLDI, SEQ ID NO:3	72	QSYDFKTYL, SEQ ID NO:45	Wu 9~	29+/-6nM
MS-BW-43	Н3	FLDI, SEQ ID NO:3	72	QSYDFINVI, SEQ ID NO:47	Mn 59∼	> 100 nM
MS-BW-44	Н3	FLDI, SEQ ID NO:3	72	QSYDFVRFM, SEQ ID NO:48	2 +/- 0.4 nM*	4+/-1 nM
MS-BW-45	Н3	FLDI, SEQ ID NO:3	12	QSYDFYKFN, SEQ ID NO:49	8 +/- 5 nM	9+/-3 nM
MS-BW-46	Н3	FLDI, SEQ ID NO:3	72	QSYDFRRFS, SEQ ID NO:50	6 +/- 3 nM	4+/-0.5 nM
MS-BW-47	Н3	FFDY, SEQ 1D NO:7	72	QSYDYQQFT, SEQ ID NO:44	~152 nM	∨ 100 nM
MS-BW-49	Н3	FFDY, SEQ ID NO:7	72	QSYDFKTYL, SEQ ID NO:45	~21 nM	Mu 001 <
MS-BW-51	H3	FFDY, SEQ ID NO:7	12	QSYDFINVI, SEQ ID NO:47	Mn <i>7∽</i>	7+/-1 nM
MS-BW-52	Н3	FFDY, SEQ ID NO:7	72	QSYDFVRFM, SEQ ID NO:48	Mn 11∽	Йи 1-/+6

* In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

Indicates preliminary data, in cases where measurement was done only once.

Affinity maturation by optimizing HCDR1 and HCDR2

[143] In the HuCAL®-Fab 1 library, only the CDRs HCDR3 and LCDR3 are diversified to a high extent. Although it is known from crystallographic studies that amino acids from these two CDRs make most of the antibody antigen contacts, the residual four CDRs are also important for antigen binding. However, their contribution to the binding energy can vary from antibody to antibody. In the HuCAL®-Fab 1 library those CDRs exhibit only a limited variability due to the presence of the different master frameworks (Knappik et al., 2000). In order to improve the affinity of the selected antibodies, an affinity maturation approach by randomizing HCDR1 and HCDR2 was applied. For this approach two affinity maturation libraries based on MS-BW-44 cloned into phage display vector pMORPH® 18 were created. In library 1, only HCDR2 of MS-BW-44 was diversified using "TRIM technology" as described in Virnekäs et al., Nucl. Acids. Res. 22, 5600-07, 1994; Knappik et al., J. Mol. Biol. 296, 57-86, 2000. In library 2, both HCDR1 and HCDR2 were diversified using the TRIM technology. In both cases, phage antibody libraries comprising 1 x 108 different clones were obtained. Both libraries were mixed and used as input for a modified AutoPan® procedure. In order to select antibodies having an increased affinity to human TIMP-1, solution panning using limiting amounts of biotinylated antigen and stringent washing conditions were applied. Antibody off rates were ranked by BIAcore™ using crude E. coli extracts of selected antibodies. Clones with slower off rate than parental clone MS-BW-44 were subjected to 1-liter scale expression and purification. Purified Fab were analyzed in BIAcore™ and human protease assay (Table 4).

Table 4. Comparison of Fab derived from HCDR1 and HCDR2 optimization with parental clone MS-BW-44

Fab	Monovalent K _D to human TIMP-1	IC ₅₀ in human protease assay*
MS-BW-44	2 +/- 0.4 nM	2 +/- 0.5 nM
MS-BW-44-2	0.5 +/- 0.2 nM	0.4 +/- 0.3 nM
MS-BW-44-6	0.6 +/- 0.2 nM	0.2 +/- 0.1 nM

^{*} IC_{50} values derived from modified protease assay using decreased amounts of TIMP-1 and MMP-1 (0.4 nM each).

[144] Clone MS-BW-44-2 was derived from library 1 thus having a modified HCDR2 cassette. Its affinity measured by BIAcoreTM was 0.5 nM. Clone MS-BW-44-6 was derived from library 2 having a modified HCDR 1 and HCDR 2 cassette and the affinity measured by BIAcoreTM was 0.6 nM. A sequence comparison between the affinity matured antibodies and their parental clones is shown in Table 8.

Table 8: Overview and sequence comparison of affinity matured Fab fragments against human TIMP-1. Sequence changes compared to parental Fab fragments (bold) are italicized

=	ı Şe ı¥	7	_	-	, t.	*	-	=	*]
IC ₅₀ In	human protease assay (nM)	11 +/- 2	4 +/- 1	0.2 +/- 0.1 *	0.4 +/- 0.3	.2 +/- (0.2 +/- 0.1 *	3 +/- (7 +/- (
Monov. Kp	to human TIMP-1 (nM)	13 +/- 2	2 +/- 0.4	0.6 +/- 0.2 0	0.5 +/- 0.2 0	0.2 +/- 0.02 0.2 +/- 0.1 *	0.3 +/- 0.1 0	0.5 +/- 0.2 0.3 +/- 0.1 *	0.2 +/- 0.04 0.2 +/- 0.1 *	e conditions
	LCDR3 sequence (SEQ ID NO:)	OSYDFLRES (47)	OSYDEVREM (48)	QSYDEVREM (48)	OSYDEVREM (48)	QSYDEVREM (48)	OSYDFVREM (48)	QSYDFVREM (48)	QSYDFIREM (365)	M under thes
	LCDR2 sequence (SEQ ID NO:)	DVSNRPS (364)	DVSNRPS (364)	DVSNRPS (364)	OVSNRPS (364) :	OVSNRPS (364)	OVSNRPS (364)	DVSNRPS (364)	DVSNRPS (364)	-BW-44 is 2 n
VL	LCDR1 sequence (SEQ ID NO:)	TGISSDVGGYNYVS (363)	TGTSSDVGGYNYVS DVSNRPS (363)	TGTSSDVGGYNYVS 1	TGTSSDVGGYNYVS DVSNRPS (363)	TGTSSDVGGYNYVS DVSNRPS (363)	TGTSSDVGGYNYVS DVSNRPS (363)	TGTSSDVGGYNYVS [TGTSSDVGGYNYVS (363)	MP-1; IC50 of MS
	Framework	VL2	VL2	VL2	VL2	VL2	VL2	VL2	VL2	IMP-1 and M
	HCDR3 sequence (SEQ ID NO:)	FLDI (3)	FLDI (3)	FLDI (3)	FLDI (3)	GLMDY (360)	МЕТН (361)	MFDV (362)	FLDI (3)	eased amounts of T
ΑМ	HCDR2 sequence (SEQ ID NO:)	AISGSGGSTYYADSVKG (357)	AISGSGGSTYYADSVKG (357)	VISGNGSNTYYADSVKG (358)	GISGNGVLIFYADSVKG (359)	GISGNGVLIFYADSVKG (359)	GISGNGVLIFYADSVKG (359)	GISGNGVLJFYADSVKG (359)	VISGNGSNTYYADSVKG (358)	protease assay using decreased amounts of TIMP-1 and MMP-1; IC, of MS-BW-44 is 2 nM under these conditions
	HCDR1 sequence (SEQ ID NO:)	GFTFSSYAMS (355)	GFTESSYAMS (355)	GETENSYAMS (356)	GETESSYAMS (355)	GFTFSSYAMS (355)	GFTFSSYAMS (355)	GFTESSYAMS (355)	GETENSYAMS (356)	* IC ₅₀ values derived from modified pro
	Frame- work	VH3	VH3	VH3	VH3	VH3	VH3	УН3	VH3	lues der
Clone	MS- BW-	8	4	44-6	44-2	44-2-4	44-2-15	44-2-16	44-6-1	* ICso va

When initially analyzed in the human TIMP-1/MMP-1 assay, it was not possible to distinguish a Fab with a sub-nanomolar affinity from a Fab with 1 nM affinity, most likely because the concentration of Fab required to reverse the inhibitory effect of human TIMP-1 on human MMP-1 activity by 50% was below the concentration of total TIMP-1 in the assay. When a modified assay was used with concentrations of TIMP-1 and MMP-1 decreased from 1.2 nM to 0.4 nM, it was possible to distinguish a 2 nM Fab from a sub-nanomolar Fab (Table 4, FIG. 8). Using this modified protease assay, MS-BW-44-2 and MS-BW-44-6 had IC₅₀ values of 0.4 nM and 0.2 nM respectively. Parental clone MS-BW-44 had an IC₅₀ of 2 nM under these conditions. Thus, by this affinity maturation approach, an affinity gain of a factor of 5 (K_d) or 5-10 (IC₅₀) was achieved.

Affinity maturation by optimizing HCDR3

[146] As mentioned above, amino acid residues in HCDR3 and LCDR3 are considered the most important for antigen binding. Taking into account that a four amino acid HCDR3 was not planned in the design of HuCAL[®]-Fab 1 and thus only occurs as a rare case due to a TRIM deletion, probably not all possible combinations of the four amino acids in HCDR3 were represented in the original HuCAL[®]-Fab 1 library. Therefore, an affinity maturation library was constructed with four and five amino acid HCDR3 maturation cassettes inserted into Fab derived from the previous maturation cycle (among them MS-BW-44-2 and MS-BW-44-6). The obtained affinity maturation library had a diversity of 1 x 10⁸ clones, therefore theoretically covering all possible four and five amino acid HCDR3 variations. Applying very stringent panning conditions, the best antibody identified, MS-BW-44-2-4, had an affinity measured by BIAcore[™] of 0.2 nM and an IC₅₀ in human TIMP-1/MMP-1 assay of 0.2 nM. A sequence comparison between the affinity matured antibodies and their parental clones is shown in Table 8. The improvement factor gained by this affinity maturation approach is 2.5 with respect to the affinity and 2 with respect to the IC₅₀.

Affinity maturation by optimizing LCDR3

- [147] As an alternative approach, a maturation strategy was used to further optimize the light chain CDR3 sequence. This was due to the fact that in the first maturation cycle where light chain exchange cloning between selected antibodies was applied, only a very limited subset of sequence variation had been exploited. Therefore, a maturation library was constructed in which, using TRIM technology, a diversified LCDR3 cassette was inserted into Fab derived from HCDR1 and HCDR2 optimization (among them MS-BW-44-2 and MS-BW-44-6). The best Fab identified with this maturation strategy was MS-BW-44-6-1 with an affinity measured by BIAcoreTM of 0.15 nM and an IC₅₀ in a human TIMP-1/MMP-1 assay of 0.2 nM. A sequence comparison between the affinity matured antibody and its parental clones is shown in Table 8. The improvement factor gained by this maturation approach is 4 with respect to affinity. A further improvement of the IC₅₀ in the protease assay could not be measured due to limitations in the assay.
- [148] As a result of a step-wise affinity maturation approach using four different maturation strategies, the monovalent affinity of an anti-human TIMP-1 specific Fab fragment was improved by a factor of 87 and its activity in human TIMP-1/MMP-1 assay by a factor of 55. The decision for defining the best Fab fragment has been made on the basis of K_d measurements using BIAcoreTM, as this method proved to be reliable for ranking antibodies with sub-nanomolar affinities, whereas the sensitivity of the human TIMP-1/MMP-1 assay was considered not suitable to rank activity of the best Fabs in the sub-nanomolar range with respect to each other.
- [149] The best Fab MS-BW-44-6-1 has an affinity measured by BIAcore™ of 0.15 nM and an IC₅₀ in human TIMP-1/MMP-1 assay of 0.2 nM. Compared to its parental clone, MS-BW-3, it has optimized LCDR3, HCDR1 and HCDR2 sequences.

EXAMPLE 18

Cross reactivity of selected anti-human TIMP-1 Fab with TIMP-2, TIMP-3, and TIMP-4

[150] TIMP-1 belongs to a family of closely related protease inhibitors all binding to various members of the MMP family of proteases. To date there are four human TIMP proteins described. To investigate potential cross-reactivity of antibody fragments selected against human TIMP-1 with other members of the human TIMP family, an ELISA was performed in which binding of antibody fragments to immobilized purified human TIMP-1, -2, -3 or -4 was analyzed (FIG. 10). Antibody fragments binding to immobilized human TIMP-1 showed no binding to human TIMP-2, -3, -4 above background level when compared to unrelated control protein BSA.

EXAMPLE 19

Generation of blocking antibodies against rat TIMP-1

[151] To generate blocking antibodies against rat TIMP-1, the HuCAL®-Fab 1 library was used for antibody selection (AutoPan®) on immobilized rat TIMP-1 followed by subcloning and expression of the selected Fab fragments in *E. coli*. Crude antibody-containing *E. coli* extracts were used for primary antibody characterization in ELISA (AutoScreen®). Purified Fab proteins were subjected to further characterization in ELISA, protease assays, and BIAcore™. Of the 8,450 selected clones were analyzed in AutoScreen®, 750 of them showed binding to rat TIMP-1. Sequence analysis revealed that in total 36 unique Fab clones specific for rat TIMP-1 were enriched during selection (Table 7). Their affinities were measured by BIAcore™ and were found to be in the range of 9 – 1000 nM (Table 7). When tested in the rat protease assay, all but one of them were able to block the interaction between rat TIMP-1 and rat MMP-13 (Table 7). The concentration of monovalent Fab needed to reverse the inhibitory effect of rat TIMP-1 on rat MMP-13 activity by 50% (IC₅₀) was in the range of 7 - 300 nM. The most active Fab

clones are MS-BW-14 (K_d 10 nM; IC₅₀ 14 nM), MS-BW-17 (K_d 13 nM; IC₅₀ 11 nM), and MS-BW-54 (K_d 9 nM; IC₅₀ 7 nM).

Table 7. Overview of anti-rat TIMP-1 Fab

i i		Framework + CDR 3 sequence	R 3 sequenc	. 9.	Monovalent K _D to	IC ₅₀ * in rat
Q P	ΛH	HCDR3	ΛΓ	LCDR3	rat TIMP-1	protease assay
MS-BW-5	HIA	GLYWAVYPYFDF, SEQ ID NO:8	16	QSRDFNRGP, SEQ ID NO:51	~210 nM	non blocking
MS-BW-6	Н3	LDTYYPDLFDY, SEQ ID NO:9	1.6	QSYDQRKW, SEQ ID NO:52	Mn 89∼	~100 nM
MS-BW-7	HIA	TYYYFDS, SEQ ID NO:10	73	QQLYGTVS, SEQ ID NO:53	~168 nM	> 300 nM
MS-BW-9	H3	YMAYMAEAIDV, SEQ ID NO:11	11	QSYDGFKTH, SEQ ID NO:54	~256 nM	> 300 nM
MS-BW-10	HIB	LVGIVGYKPDELLYFDV, SEQ ID NO:12	73	QSYDYSLL, SEQ ID NO:55	~200 nM	~ 30 nM
MS-BW-11	H3	YGAYFGLDY, SEQ ID NO:13	73	QSYDFNFH, SEQ ID NO:56	~200 nM	>300 nM
MS-BW-12	9H	GYADISFDY, SEQ ID NO:14	32	QSYDMIARYP, SEQ ID NO:57	~419 nM	>300 nM
MS-BW-13	H3	YYLLLDY, SEQ ID NO:15	73	QSWDIHPFDV, SEQ ID NO:58	~939 nM	not tested
MS-BW-14	HIA	WSDQSYHYYWHPYFDV, SEQ ID NO:16	1.6	QSWDLEPY, SEQ ID NO:59	10 +/- 5 nM	14+/-3 nM
MS-BW-15	Н3	LIGYFDL, SEQ ID NO:17	12	QSYDVLDSE, SEQ ID NO:60	~80 nM	~ 200 nM
MS-BW-17	HS	LTNYFDSIYYDH, SEQ ID NO:18	3.5	QSYDPSHPSK, SEQ ID NO:61	13 +/- 3 nM	11+/-3 nM
MS-BW-18	HS	LVGGGYDLMFDS, SEQ ID NO:19	72	QSYDDMQF, SEQ ID NO:62	~153 nM	> 300 nM
MS-BW-19	HS	YVTYGYDDYHFDY, SEQ ID NO:20	72	QSWDINHAI, SEQ ID NO:63	~187 nM	> 300 nM
MS-BW-20	ніА	SGYLDY, SEQ ID NO:21	3.5	QSYDYYDYG, SEQ ID NO:64	~70 nM	> 300 nM

MS-BW-21	HIA	YIGYTNVMDIRPGYFLDY, SEQ ID NO:22	73	QQANDFPI, SEQ ID NO:65	36 +/- 2 nM	67+/-5nM
MS-BW-22	HS	FRAYGDDFYFDV, SEQ ID NO:23	7.2	QSWDNLKMPV, SEQ ID NO:66	35 nM	65+/-11 nM
MS-BW-23	HIB	JMWSDYGQLVKGGDI, SEQ ID NO:24	12	QSYDVFPINR, SEQ ID NO:67	~207 nM	> 300 nM
MS-BW-24	HS	YYVTDTAYFDY, SEQ ID NO:25	72	QSDLYFP, SEQ ID NO:68	Z3 nM	20+/-1 nM
MS-BW-29	HS	HDFDGSIFMDF, SEQ ID NO:26	3 2	QSYDVTPR, SEQ ID NO:69	~214 nM	>100 nM
MS-BW-30	НЅ	YAGHQYEFFFDF, SEQ ID NO:27	? 3	QSRDPVGFP, SEQ ID NO:70	Wu 9€~	>100 nM
MS-BW-31	HS	LYADADIYFDY, SEQ ID NO:28	12	QSYDLSPR, SEQ ID NO:71	~13 +/- 9 nM	>100 nM
MS-BW-32	HIA	TKYVGSEDV, SEQ ID NO:29	12	QSYDFSHYFF, SEQ ID NO:72	~92 nM	> 100 nM
MS-BW-36	HS	YRYPHMFDF, SEQ ID NO:30	13	QSYDLRYSH, SEQ ID NO:73	~42 nM	~75 nM
MS-BW-37	HS	LFAGLELYFDY, SEQ ID NO:31	3.2	QSYDLRNR, SEQ ID NO:74	10 +/- 9 nM	>100 nM
MS-BW-38	H3	GGFFNMDY, SEQ ID NO:32	3.2	QSYDFTYGS, SEQ ID NO:75	~353 nM	>300 nM
MS-BW-39	HIA	GYIPYHLFDY, SEQ ID NO:33	13	QQFNDSPY, SEQ ID NO:76	~108 nM	>100 nM
MS-BW-54	HS	YYGFEYDLLFDN, SEQ ID NO:34	26	QSYDISGYP, SEQ ID NO:77	9 +/- 1 nM	7 nM
MS-BW-55	нів	ITYIGYDF, SEQ ID NO:35	7 i	QSRDLYYVYY, SEQ ID NO:78	~23 nM	~ 100 nM
MS-BW-56	HIA	QEWYMDY, SEQ ID NO:36	<i>i</i> 3	QSYDRSMW, SEQ ID NO:79	~170 nM	> 100 nM
MS-BW-57	Н5	LYPEDLIYFDY, SEQ ID NO:37	7 i	QSWDVQTDK, SEQ ID NO:80	~39 aM	~60 nM
MS-BW-58	9H	WMTPPGHYYGYTFDV, SEQ ID NO:38	£ i	QSWDPSHYY, SEQ ID NO:81	~138 nM	not tested
MS-BW-59	HS	LRVHDYAMYFDL, SEQ ID NO:39	3.2	QSYDIMPER, SEQ ID NO:82	~15 nM	30 +/- SnM

MS-BW-60		H5 FVSYNGSVPYFDY, SEQ ID NO:40	12	? 2 QSMDFRLMH, SEQ ID NO:83	~30 nM	> 100 nM
MS-BW-61	SH	IIGDYVIFFDV, SEQ ID NO:41	? 2	? 2 QSFDMIHPY, SEQ ID NO:84	Mn 12∽	> 100 nM
MS-BW-62	SH	LFTYPFLYFDV, SEQ ID NO:42	22	QSDFPVM, SEQ ID NO:85	Ма ∂5∽	19 +/- 2
MS-BW-63	SH	ILTGHVLLFDY, SEQ ID NO:43	3.2	QSDNPYL, SEQ ID NO:86	~14 nM	20 +/- InM

* In cases were standard deviations are given, three independent measurements were done with Fab from three different protein expressions/purifications.

Indicates preliminary data, in cases where measurement was done only once.

EXAMPLE 20

Increasing the affinity of selected anti-rat TIMP-1 antibodies

- [152] Affinity maturation was applied to increase the affinity of monovalent anti-rat TIMP-1 Fab fragments to the sub-nanomolar range. No clear sequence homology could be identified among the light chain CDR3 sequences of the selected antibody fragments, indicating that an optimal light chain CDR3 sequence was probably not present or had not been selected from the original HuCAL®-Fab 1 library. We therefore started with modification of LCDR3 to increase the affinity of Fabs.
- [153] Two affinity maturation libraries based on MS-BW-14, -17, and -54 cloned into phage display vector pMORPH® 18 were created. In library 1, only LCDR3 was diversified using TRIM technology, as described in Virnekäs et al., Nucl. Acids. Res. 22, 5600-07, 1994; Knappik et al., J. Mol. Biol. 296, 57-86, 2000. In library 2, LCDR1, LCDR2, and LCDR3 were diversified simultaneously using the TRIM technology, while the connecting framework regions were kept constant. In both cases, phage antibody libraries comprising 3 x 10⁸ different clones were obtained. Both libraries were mixed and used as input for a modified AutoPan® procedure. To select antibodies having an increased affinity to rat TIMP-1, solution panning using limiting amounts of biotinylated antigen and stringent washing conditions were applied.
- [154] Antibody-off-rates were ranked by BIAcoreTM using crude *E. coli* extracts. Clones with slower off rate than parental clones MS-BW-14, -17, or -54 were subjected to expression and purification in 1-liter scale. Purified Fab were analyzed in BIAcoreTM and rat protease assays (Table 6). MS-BW-17-1 (K_d 0.8 nM, IC₅₀ 1.6 nM), MS-BW-17-2 (K_d 1.3 nM, IC₅₀ 1.1 nM), and MS-BW-17-3 (K_d 1.9 nM, IC₅₀ 3 nM) were derived from affinity maturation library 1 having an optimized LCDR3 sequence, whereas MS-BW-

54-1 (K_d 2 nM, IC₅₀ 3 nM) was derived from affinity maturation library 2 having an optimized LCDR1, -2, and -3 sequence (Table 9).

Table 9. Overview and sequence comparison of affinity matured Fab fragments against rat TIMP-1. Sequence changes compared to parental Fab fragments (bold) are italicized.

	<u> </u>							
IC ₅₀ in	rat protease assay (nM)	14 +/- 3	11 +/- 3	7	1.6	1.1	ю	<u>س</u>
Monov.	K _D to rat TIMP-1 (nM)	10 +/- 5	13 +/- 3	1-/+ 6	8.0	1.3	6.1	7 .
	LCDR3 sequence (SEQ ID NO:)	QSWDLEPY (59)	QSYDPSHPS K (61)	QSYDISGYP (77)	QAFDVAPNG K (376)	OAFAVMPNV E (377)	QS <i>FTVSPGA</i> D (378)	QAYDSSGYP (379)
ָר	LCDR2 sequence (SEQ ID NO:)	imiydnnqrps (373)	LMIYDVSNRPS (374)	<i>lm</i> iydvsnrps (374)	LMIYDVSNRPS QAFDVAPNG (374) K (376)	LMIYDVSNRPS (374)	LMIYDVSNRPS QS <i>FTVSPGA</i> (374) D (378)	LMIYAGNNRPS (375)
۸۲	Frame- LCDR1 sequence work (SEQ ID NO:)	SGSSSNIGSNYVS (371)	TGTSSDVGGYNYVS (363)	TGTSSDVGGYNYVS (363)	TGTSSDVGGYNYVS (363)	TGTSSDVGGYNYVS (363)	TGTSSDVGGYNYVS (363)	TGTSSDLGGYNYVS (372)
	Frame- work	ιτα	VL2	VL2	VL2	VL2	VL2	VL2
	HCDR3 sequence (SEQ ID NO:)	WSDQSYHYYWHPYFDV (370)	LINYFDSIYYDH (18)	XYGFEYDILFDN (34)	LTNYFDSIYYDH (18)	LTNYFDSIYYDH (18)	LTNYFDSIYYDH (18)	YYGFEYDLLFDN (34)
ΝΉ	HCDR2 sequence (SEQ ID NO:)	giipifgtanyaqkeqg (368)	IIYPGDSDTRYSPSFQG (369)	LIXPGDSDTRYSBSFQG (369)	(369)	IIYPGDSDTRYSPSFQG (369)	IIYPGDSDTRYSPSFQG (369)	IIYPGDSDTRYSPSFQG (369)
	Clone (MS- Frame- HCDR1 sequence BW-) work (SEQ ID NO:)	GGTFSSYAIS (366)	GYSFTSYWIG (367)	GYSFTSYWIG (367)	GYSFTSYWIG (367)	GYSFTSYWIG (367)	GYSFTSYWIG (367)	GYSFTSYWIG (367)
	Frame- work	VH1A	VH5	VH5	VH5	VH5	VH5	VH5
	Clone (MS-BW-)	14	17	54	17-1	17-2	17-3	54-1

[155] The improvement gained by these different one-step maturation strategies was up to a factor of 16.3 with regard to affinity and 10 with regard to functional activity in the protease assay.

EXAMPLE 21

Conversion of anti-TIMP-1 Fab fragments into human IgG_1 molecules for use in the rat model of chronic carbon tetrachloride-induced liver fibrosis

- [156] Anti-TIMP-1 Fab fragments were converted into human IgG1 molecules to create antibody molecules with prolonged *in vivo* half-lives for the use in the rat model of chronic carbon tetrachloride-induced liver fibrosis. This was done by cloning the heavy and light chain variable regions of the Fab into two separate vectors for mammalian IgG₁ expression (Krebs *et al.*, 2001)
- [157] Anti-rat TIMP-1 clone MS-BW-14 was chosen for the first *in vivo* study, and IgG₁ protein was produced by transient expression. Anti-human TIMP-1 clone MS-BW-3 was selected as a negative control IgG₁ and was also produced by transient expression. Purified IgG₁ proteins MS-BW-14 and MS-BW-3 were subjected to quality control in BIAcoreTM and rat TIMP-1/rat MMP-13 assays. Bivalent affinity for rat TIMP-1 measured in BIAcoreTM (chip density 500 RU, fitting model for bivalent analyte) is 0.2 nM for MS-BW-14, compared to 13 nM for the corresponding monovalent Fab fragment. This increase in affinity for the IgG₁ is due to the avidity effects caused by binding of bivalent IgG₁ to immobilized rat TIMP-1 protein on the BIAcoreTM chip. As expected, the negative control IgG₁ MS-BW-3 showed no binding to rat TIMP-1 but bound to human TIMP-1 with a bivalent affinity of approximately 0.4 nM.
- [158] FIG. 12 shows the activity of MS-BW-14 Fab and IgG₁ and MS-BW-3 IgG₁ in a rat TIMP-1/rat MMP-13 assay. The IC₅₀ of MS-BW-14 Fab and IgG₁ are nearly identical. The avidity effect seen in BIAcoreTM does not occur in this assay because, in contrast to

the BIAcoreTM experiment, this assay is based on a monovalent interaction in solution between TIMP-1 and the IgG₁. As expected, MS-BW-3 has no effect on rat TIMP-1 binding to rat MMP-13 and thus is a suitable negative control for a rat *in vivo* study.

[159] Affinity matured clone MS-BW-17-1 was then converted from a monovalent Fab fragment to a bivalent IgG₁. Protein was produced by stable transfection. Purified protein was subjected to quality control in BIAcoreTM and rat TIMP-1/rat MMP-13 assays (FIG. 13). In BIAcoreTM an increased bivalent affinity (avidity) of 0.04 nM for IgG₁ compared to 0.8 nM for monovalent Fab fragment was seen, whereas the activity in the rat TIMP-1/rat MMP-13 assay was comparable for IgG₁ and Fab as expected.

EXAMPLE 22

Cross-reactivity of anti-rat TIMP-1 IgG1 MS-BW-17-1 with mouse TIMP-1

[160] Species cross-reactivity of MS-BW-17-1 IgG₁ and Fab with mouse TIMP-1 was determined by BIAcore™ to investigate the feasibility of alternative *in vivo* models that use mice instead of rats. Although MS-BW-17-1 clearly bound to mouse TIMP-1 immobilized to the chip surface, the affinity of both Fab (180 nM) and IgG₁ (9 nM) was 225-fold weaker than the affinity to rat TIMP-1. As the interaction between mouse TIMP-1 and BW-17-1 IgG₁ in serum is most likely monovalent, the affinity of BW-17-1 Fab probably reflects the "real" affinity of this interaction. Therefore, the Fab affinity value should be considered when calculating the feasibility of using BW-17-1 IgG₁ in a mouse *in vivo* study.

EXAMPLE 23

Effect of Timp-1 antibody on the development of bleomycin-induced pulmonary fibrosis

- [161] The following example demonstrates the ability of a human anti-rat Timp-1 antibody (BW17.1) to prevent fibrotic collagen deposition in a bleomycin-induced rat lung fibrosis model.
- [162] Male Lewis rats (6 weeks of age) received a single intratracheal challenge with bleomycin (0.3 mg/rat, in saline) or vehicle (saline) on day 0. Fourteen days later, animals were euthanized, the lung excised, fixed, and processed for evaluation of lung fibrosis. Lung tissue sections were cut, and quantitative assessment by image analysis of lung collagen in lung tissue sections stained with Mason Trichrome stain performed.
- [163] Antibody administration: A 20 mg/kg dose of human ant-rat TIMP-1 antibody or control human antibody (IgG) was administered subcutaneously on day -1. Subsequently, a 10mg/kg dose of human ant-rat TIMP-1 antibody or control human antibody (IgG) was administered s.c. on days 2, 5, 8, and 11. The following five groups of animals were studied: Saline i.t. challenge + antibody vehicle (PBS); Saline i.t. challenge + TIMP-1 antibody; Bleomycin i.t. challenge + antibody vehicle (PBS); Bleomycin i.t. challenge + control antibody.
- [164] FIG. 14 shows the effect of the inhibitory effect of TIMP-1 antibody on bleomycininduced lung fibrotic collagen.

EXAMPLE 24

Effect of BW-14 anti-TIMP-1 antibody in a rat model with CCl4-induced liver fibrosis

[165] Carbon tetrachloride (CCl₄) was used to induce liver fibrosis as described in Example 9.

A single intravenous dose of 3 mg/kg BW-14 or control antibody BW-3, respectively,

was administered on day 19. At this time, total liver collagen (hydroxyproline determined according to Prockop and Udenfried) is already significantly increased by CCl₄, and fibrotic collagen rapidly accumulates during the following weeks. The rats were sacrificed on day 28. The treatment groups were: no CCl₄ + control antibody BW 3 (n=10 rats), CCl₄ + control antibody BW 3 (n=20 rats), and CCl₄ + BW 14 (n=20 rats).

[166] The effect of control vs. TIMP-1 antibody as reflected in morphometric measurements of fibrous collagen (Sirius Red stained area as percentage of the total field) is shown in FIG. 15. Comparison of both control antibody treated groups shows that CCl₄ caused an approximately three-fold increase in collagen area. BW-14 antibody treatment reduced the pathological collagen increment by 26%. The lower fibrous collagen value of the CCl₄ + BW-14 group compared to the CCl₄ + BW-3 group was statistically significant (p< 0.05, Kolmogorow-Smirnow test).</p>

REFERENCES

- [167] Ausubel et al. (1998) Current Protocols in Molecular Biology. Wiley, New York, USA.
- [168] Better et al., (1988) Escherichia coli secretion of an active chimeric antibody fragment. Science 240, 1041.
- [169] Bruggeman et al., (1996) Phage antibodies against an unstable hapten: oxygen sensitive reduced flavin. FEBS Lett. 388, 242.
- [170] Butler et al., (1999) Human tissue inhibitor of metalloproteinases 3 interacts with both the N- and C-terminal domains of gelatinases A and B. Regulation by polyanions. J Biol Chem. 274, 10846.
- [171] Gomis-Ruth *et al.*, (1996). Mechanism of inhibition of the human matrix metalloproteinase stromelysin-1 by TIMP-1. Nature. 389, 77.

[172] Griffiths, A.D. and Duncan, A.R. (1998) Strategies for selection of antibodies by phage display. Curr. Opin. Biotechnol. 9, 102.

- [173] Hoogenboom, H.R. and Winter, G. (1992). By-passing immunisation. Human antibodies from synthetic repertoires of germline VH gene segments rearranged *in vitro*. J. Mol. Biol. 227, 381.
- [174] Iredale *et al.*, (1996) Tissue inhibitor of metalloproteinase-1 messenger RNA expression is enhanced relative to interstitial collagenase messenger RNA in experimental liver injury and fibrosis. Hepatology. 24, 176.
- [175] Knappik et al., (2000) Fully synthetic human combinatorial antibody libraries (HuCAL) based on modular consensus frameworks and CDRs diversified with trinucleotides. J. Mol. Biol. 296, 55.
- [176] Krebs et al., (2001) High-throughput generation and engineering of recombinant human antibodies. J Immunol Methods. 254, 67.
- [177] Lowman, H.B. (1997) Bacteriophage display and discovery of peptide leads for drug development. Annu. Rev. Biophys. Biomol. Struct. 26, 401.
- [178] McCafferty et al., (1990) Phage antibodies: filamentous phage displaying antibody variable domains. Nature 348, 552.
- [179] Meng et al., (1999) Residue 2 of TIMP-1 is a major determinant of affinity and specificity for matrix metalloproteinases but effects of substitutions do not correlate with those of the corresponding P1' residue of substrate. J Biol Chem. 274, 10184.
- [180] Meulemans *et al.*, (1994) Selection of phage-displayed antibodies specific for a cytoskeletal antigen by competitive elution with a monoclonal antibody. J. Mol. Biol. 244, 353.

[181] Miyazaki et al., (1999) Changes in the specificity of antibodies by site-specific mutagenesis followed by random mutagenesis. Protein Eng. 12, 407.

- [182] Sheets et al., (1998) Efficient construction of a large nonimmune phage antibody library: The production of high-affinity human single-chain antibodies to protein antigens. Proc. Natl. Acad. Sci. U.S.A. 95, 6157.
- [183] Skerra, A. and Plückthun, A. (1988) Assembly of a functional immunoglobulin Fv fragment in Escherichia coli. Science 240, 1038.
- [184] Smith, G.P. (1985) Filamentous fusion phage: novel expression vectors that display cloned antigens on the virion surface. Science 228, 1315.
- [185] Smith, G.P. and Petrenko, V.A. (1997) Phage display. Chem. Rev. 97, 391.
- [186] Stausbøl-Grøn et al.(1996) A model phage display subtraction method with potential for analysis of differential gene expression. FEBS Lett. 391, 71.
- [187] Virnekäs et al. (1994) Trinucleotide phosphoramidites: ideal reagents for the synthesis of mixed oligonucleotides for random mutagenesis. Nucl. Acids Rès. 22, 5600.

CLAIMS

A purified preparation of a human antibody, wherein the antibody:
 binds to a tissue inhibitor of metalloprotease-1 (TIMP-1); and
 neutralizes a matrix metalloprotease (MMP)-inhibiting activity of the TIMP-1.

- 2. The preparation of claim 1 wherein the MMP is human MMP-1.
- 3. The preparation of claim 2 wherein the MMP is rat MMP-13.
- 4. The preparation of claim 1 wherein the TIMP-1 is a human TIMP-1.
- 5. The preparation of claim 4 wherein the antibody binds to the human TIMP-1 with a K_d selected from the group consisting of about 0.1 nM to about 10 μ M, about 2 nM to about 1 μ M, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 0.2 nM to about 13 nM, about 0.5 nM to about 2 nM to about 13 nM, and about 0.5 nM to about 2 nM.
- 6. The preparation of claim 4 wherein the antibody binds to the human TIMP-1 with a K_d selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.5 M, about 0.6 nM, about 2 nM, about 7 nM, about 10 nM, about 11 nM, and about 13 nM.
- 7. The preparation of claim 4 wherein the antibody neutralizes the MMP-inhibiting activity of the human TIMP-1 with an IC₅₀ selected from the group consisting of about .1 nM to about 200 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 0.2 nM to about 11 nM, about 0.2 nM to about 4 nM, and about 4 nM to about 11 nM.

8. The preparation of claim 4 wherein the antibody neutralizes the MMP-inhibiting activity of the human TIMP-1 with an IC₅₀ selected from the group consisting of about 0.2 nM, about 0.3 nM, about 0.4 nM, about 4 nM, about 7 nM, about 9 nM, and about 11 nM.

- 9. The preparation of claim 4 wherein the K_d for binding to human TIMP-1 and the IC₅₀ for neutralizing the MMP-inhibiting activity of the human TIMP-1 are approximately equal.
 - 10. The preparation of claim 1 wherein the TIMP-1 is a rat TIMP-1.
- 11. The preparation of claim 10 wherein the antibody binds to the rat TIMP-1 with a K_d selected from the group consisting of about 0.1 nM to about 10 μM, about 2 nM to about 1 μM, about 2 nM to about 200 nM, about 2 nM to about 150 nM, about 50 nM to about 100 nM, about 1.3 nM to about 13 nM, about 1.8 nM to about 10 nM, about 2 nM to about 9 nM, about 1.3 nM to about 9 nM, and about 2 nM to about 10 nM.
- 12. The preparation of claim 10 wherein the antibody binds to the rat TIMP-1 with a K_d selected from the group consisting of about 0.8 nM, about 1 nM, about 1.3 nM, about 1.9 nM, about 2 nM, about 3 nM, about 9 nM, about 10 nM, about 13 nM, about 14 nM, and about 15 nM.
- 13. The preparation of claim 10 wherein the antibody neutralizes the rat TIMP-1 activity with an IC₅₀ selected from the group consisting of about .1 nM to about 300 nM, about 1 nM to about 100 nM, about 2 nM to about 50 nM, about 5 nM to about 25 nM, about 10 nM to about 15 nM, about 1.1 nM to about 14 nM, about 1.6 nM to about 11 nM, about 3

nM to about 7 nM, about 1.1 nM to about 7 nM, about 1.1 nM to about 11 nM, about 3 nM to about 11 nM, and about 3 nM to about 14 nM.

- 14. The preparation of claim 10 wherein the antibody neutralizes the rat TIMP-1 activity with an IC₅₀ selected from the group consisting of about 1.1 nM, about 1.6 nM, about 3 nM, about 7 nM, about 11 nM, about 14 nM, about 19 nM, about 20 nM, about 30 nM, and about 100 nM.
- 15. The preparation of claim 10 wherein the K_d for binding to rat TIMP-1 and the IC_{50} for neutralizing the MMP-inhibiting activity of the rat TIMP-1 are approximately equal.
- 16. A purified preparation of a human antibody which comprises a VHCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360.
- 17. A purified preparation of a human antibody which comprises a VLCDR3 region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379.
- 18. A purified preparation of a human antibody which comprises a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:7 and 48, SEQ ID NOS:7 and 52, SEQ ID NOS:10

and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

19. A purified preparation of a human antibody comprising a VHCDR3 and VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID

NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

- 20. The purified preparation of claim 19 wherein the human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.
- 21. The purified preparation of claim 19 wherein the human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.
- 22. A purified preparation of a human antibody which comprises a heavy chain and a light chain amino acid pair selected from the group consisting of SEQ ID NOS:140 and 97, SEQ ID NOS:141 and 98, SEQ ID NOS:142 and 99, SEQ ID NOS:143 and 100, SEQ ID NOS:144 and 101, SEQ ID NOS:145 and 102, SEQ ID NOS:146 and 103, SEQ ID NOS:142 and 97, SEQ ID NOS:142 and 98, SEQ ID NOS:142 and 100, SEQ ID NOS:142 and 101,

SEQ ID NOS:142 and 102, SEQ ID NOS:142 and 103, SEQ ID NOS:146 and 97, SEQ ID NOS:146 and 98, SEQ ID NO:146 and 100, SEQ ID NOS:146 and 101, SEQ ID NOS:148 and 104, SEQ ID NOS:148 and 105, SEQ ID NOS:149 and 106, SEQ ID NOS:150 and 107, SEQ ID NOS:151 and 108, SEQ ID NOS:152 and 109, SEQ ID NOS:153 and 110, SEQ ID NOS:154 and 111, SEQ ID NOS:155 and 112, SEQ ID NOS:156 and 113, SEQ ID NOS:157 and 114, SEQ ID NOS:158 and 115, SEQ ID NOS:159 and 116, SEQ ID NOS:160 and 117, SEQ ID NOS:161 and 118, SEQ ID NOS:162 and 119, SEQ ID NOS:163 and 120, SEQ ID NOS:164 and 121, SEQ ID NOS:165 and 122, SEQ ID NOS:166 and 123, SEQ ID NOS:167 and 124, SEQ ID NOS:168 and 125, SEQ ID NOS:169 and 126, SEQ ID NOS:170 and 127, SEQ ID NOS:171 and 128, SEQ ID NOS:172 and 129, SEQ ID NOS:173 and 130, SEQ ID NOS:174 and 131, SEQ ID NOS:175 and 132, SEQ ID NOS:176 and 133, SEQ ID NOS:177 and 134, SEQ ID NOS:178 and 135, SEQ ID NOS:179 and 136, SEQ ID NOS:180 and 137, SEQ ID NOS:181 and 138, and SEQ ID NOS:182 and 139.

- 23. A pharmaceutical composition comprising:
- a human antibody which (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1; and
 - a pharmaceutically acceptable carrier.
 - 24. The pharmaceutical composition of claim 23 wherein the MMP is human MMP-1.
 - 25. The pharmaceutical composition of claim 23 wherein the MMP is rat MMP-13.
- 26. The pharmaceutical composition of claim 23 wherein the TIMP-1 is a human TIMP-1.

27. The pharmaceutical composition of claim 23 wherein the TIMP-1 is a rat TIMP-1.

- 28. The pharmaceutical composition of claim 23 wherein a K_d for binding to the TIMP-1 and an IC₅₀ for neutralizing the MMP-1-inhibiting activity of the TIMP-1 are approximately equal.
- 29. A purified polynucleotide which encodes a human antibody comprising a VHCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-43 and 360, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- 30. The purified polynucleotide of claim 31 wherein the VHCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:227-269.
- 31. A purified polynucleotide which encodes a human antibody comprising a VLCDR3 region which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:44-86 and 365-379, wherein the human antibody (1) binds to a TIMP-1 and (2) neutralizes an MMP-inhibiting activity of the TIMP-1.
- 32. The purified polynucleotide of claim 31 wherein the VLCDR3 region is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:184-226.
- 33. The purified polynucleotide of claim 31 wherein the human antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:140-182.
- 34. The purified polynucleotide of claim 33 wherein the heavy chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:269-311.

35. The purified polynucleotide of claim 33 wherein the human antibody comprises a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOS:97-139.

- 36. The purified polynucleotide of claim 35 wherein the light chain is encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOS:312-354.
 - 37. An expression vector comprising the polynucleotide of claim 29.
 - 38. An expression vector comprising the polynucleotide of claim 30.
 - 39. An expression vector comprising the polynucleotide of claim 31.
 - 40. An expression vector comprising the polynucleotide of claim 32.
 - 41. An expression vector comprising the polynucleotide of claim 33.
 - 42. An expression vector comprising the polynucleotide of claim 34.
 - 43. An expression vector comprising the polynucleotide of claim 35.
 - 44. An expression vector comprising the polynucleotide of claim 36.
 - 45. A host cell comprising the expression vector of claim 37.
 - 46. A host cell comprising the expression vector of claim 38.
 - 47. A host cell comprising the expression vector of claim 39.
 - 48. A host cell comprising the expression vector of claim 40.
 - 49. A host cell comprising the expression vector of claim 41.
 - 50. A host cell comprising the expression vector of claim 42.
 - 51. A host cell comprising the expression vector of claim 43.
 - 52. A host cell comprising the expression vector of claim 44.

53. A method of making a human antibody, comprising the steps of: culturing the host cell of claim 45 under conditions whereby the antibody is expressed; and

purifying the human antibody from the host cell culture.

- 54. The method of claim 55 wherein the expression vector comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOS:183-357.
- 55. A method of decreasing an MMP-inhibiting activity of a TIMP-1, comprising the step of:

contacting the TIMP-1 with a human antibody that binds to the TIMP-1, whereby the MMP-inhibiting activity of the TIMP-1 is decreased relative to MMP-inhibiting activity of the TIMP-1 in the absence of the antibody.

- 56. The method of claim 55 wherein the MMP is human MMP-1.
- 57. The method of claim 55 wherein the MMP is rat MMP-13.
- 58. The method of claim 55 wherein the TIMP-1 is a human TIMP-1.
- 59. The method of claim 55 wherein the TIMP-1 is a rat TIMP-1.
- 60. The method of claim 55 wherein the step of contacting is carried out in a cell-free system.
- 61. The method of claim 55 wherein the step of contacting is carried out in a cell culture system.
 - 62. The method of claim 55 wherein the step of contacting is carried out in vivo.

63. The method of claim 55 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

64. A method of ameliorating symptoms of a disorder in which TIMP-1 is elevated, comprising the step of:

administering to a patient having the disorder an effective amount of a human antibody which neutralizes an MMP-inhibiting activity of the TIMP-1, whereby symptoms of the disorder are ameliorated.

- 65. The method of claim 64 wherein the MMP is human MMP-1.
- 66. The method of claim 64 wherein the MMP is rat MMP-13.
- 67. The method of claim 64 wherein the disorder is selected from the group consisting of liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute coronary syndrome, lupus nephritis, glomerulosclerotic renal disease, idiopathic pulmonary fibrosis, benign prostate hypertrophy, lung cancer, and colon cancer.
- 68. The method of claim 64 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:7 and 48, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71,

SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEQ ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

- 69. A method of detecting a TIMP-1 in a test preparation, comprising the steps of:

 contacting the test preparation with a human antibody that specifically binds to
 the TIMP-1; and
 - assaying the test preparation for the presence of an antibody-TIMP-1 complex.
 - 70. The method of claim 69 wherein the antibody comprises a detectable label.
 - 71. The method of claim 69 wherein the antibody is bound to a solid support.
- 72. The method of claim 69 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEQ ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:7 and 48, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID

NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEQ ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEQ ID NOS:40 and 83, SEQ ID NOS:41 and 84, SEQ ID NOS:42 and 85, and SEQ ID NOS:43 and 86.

73. A method to aid in diagnosing a disorder in which a TIMP-1 level is elevated, comprising the steps of:

contacting a sample from a patient suspected of having the disorder with a human antibody that binds to TIMP-1; and

assaying for the presence of an antibody-TIMP-1 complex, whereby detection of an amount of the complex which is greater than an amount of the complex in a normal sample identifies the patient as likely to have the disorder.

- 74. The method of claim 73 wherein the antibody comprises a detectable label.
- 75. The method of claim 73 wherein the antibody is bound to a solid support.
- 76. The method of claim 73 wherein the antibody comprises a VHCDR3 and a VLCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOS:1 and 44, SEQ ID NOS:2 and 45, SEQ ID NO:3 and 46, SEQ ID NOS:4 and 47, SEQ ID

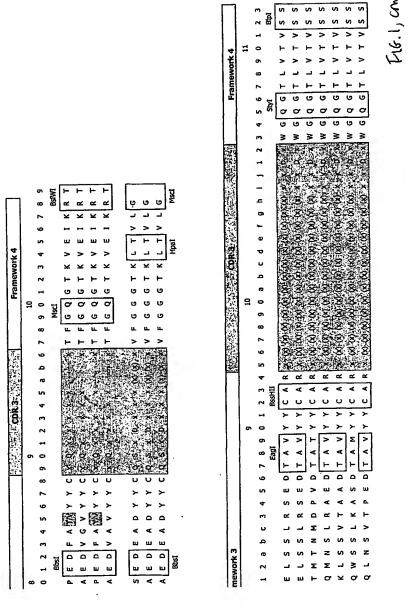
NOS:5 and 48, SEQ ID NOS:6 and 49, SEQ ID NOS:7 and 50, SEQ ID NOS:3 and 44, SEQ ID NOS:3 and 45, SEQ ID NOS:3 and 47, SEQ ID NOS:3 and 48, SEQ ID NOS:3 and 49, SEO ID NOS:3 and 50, SEQ ID NOS:7 and 44, SEQ ID NOS:7 and 45, SEQ ID NOS:7 and 47, SEQ ID NOS:7 and 48, SEQ ID NOS:8 and 51, SEQ ID NOS:9 and 52, SEQ ID NOS:10 and 53, SEQ ID NOS:11 and 54, SEQ ID NOS:12 and 55, SEQ ID NOS:13 and 56, SEQ ID NOS:14 and 57, SEQ ID NOS:15 and 58, SEQ ID NOS:16 and 59, SEQ ID NOS:17 and 60, SEQ ID NOS:18 and 61, SEQ ID NOS:19 and 62, SEQ ID NOS:20 and 63, SEQ ID NOS:21 and 64, SEQ ID NOS:22 and 65, SEQ ID NOS:23 and 66, SEQ ID NOS:24 and 67, SEQ ID NOS:25 and 68, SEQ ID NOS:26 and 69, SEQ ID NOS: 27 and 70, SEQ ID NOS:28 and 71, SEO ID NOS:29 and 72, SEQ ID NOS:30 and 73, SEQ ID NOS:31 and 74, SEQ ID NOS:32 and 75, SEQ ID NOS:33 and 76, SEQ ID NOS:34 and 77, SEQ ID NOS:35 and 78, SEQ ID NOS:36 and 79, SEQ ID NOS:37 and 80, SEQ ID NOS:38 and 81, SEQ ID NOS:39 and 82, SEO ID NOS:40 and 83, SEO ID NOS:41 and 84, SEQ ID NOS:42 and 85, SEQ ID NOS:43 and 86, SEQ ID NOS:3 and 48, SEQ ID NOS:360 and 48, SEQ ID NOS:3 and 365, SEQ ID NOS:16 and 59, SEO ID NOS:18 and 61, SEQ ID NOS:34 and 77, SEQ ID NOS:34 and 379, SEQ ID NOS:18 and 376, SEQ ID NOS:18 and 377, and SEQ ID NOS:18 and 378.

- 77. The method of claim 73 wherein the sample is obtained from a tissue selected from the group consisting of colon, liver, heart, kidney, prostate, serum, and lung.
- 78. The method of claim 73 wherein the disorder is selected from the group consisting of liver fibrosis, alcoholic liver disease, cardiac fibrosis, acute cardiac syndrome,

lupus nephritis, glomerulosclerotic renal disease, benign prostate hypertrophy, lung cancer, colon cancer, and idiopathic pulmonary fibrosis.

Sequence Summary HuCAL Libraries scFv1, scFv2, scFv3 and Fab1 CONTRACTOR OF STREET Position Position ¥ VH1A VH1B VH2 VH4 VH5 VL3.2 VL3.3 VL3.3 VLK1 VLK2 VLK3 VLK4 7

1		6		ø	ш	ш	o		o	o	o		ال	Ēl	8	0		Σ	Σ	_	_	_	د	_	
		œ		_	>	يد	_		_	_	\vdash			1		0		> -	>	>	>	S	>-	S	
		7		s	œ	s	S		G	ø	Ø		ļ	-1		80		∢	¥	>		u.	⋖	u.	
		9		s	Ŋ	S	S)	v	S			-		^		-	-	o	۲	ď	!-	o	
		ĸ		-	1	-	-		-	-	-		l	1		9		S	s -	z	z	z	S	z	
12		4		-	¥	۲	-		4	۲	۲		l	١		S	NSP.	-	- 1	¥	¥	×	-	~	
١١١		m		_	_	_	_		_	_	_		,	j		4	ž	S	٣L	Ľ	s	S	٧Į	<u>~</u>	
Framework 3		7		۲	۲	۳	⊢		S	v	۲		1	١		m		ш	-	-	Z	-	×	Ή.	
[2]		-		u_	u.	•	ts.		*	⋖	4		ŀ	ı		7		۵	0	۵	۵	٥	٥	۵	
	^	0		٥	٥	۵	۵		S	۲	۲		į.	-1		-		⋖	~	×	œ	>	⋖	۵.	
		0		-	۲	۲	-		H	z	z			- [7	0		μ-	-	S	S	S	S	z	
		œ		b	v	U	و		G	U	ט			- [6	f	_	Σ			-	ᆵ	- -	
		7	BamHI	S	S	S	S.		S	S	Ŋ			-		8		-		۲.	_	>	7		
		9	쫎	ဖ	b	U	9	j	<u>~</u>	×	z		1	Ì			ا ۵	<u>></u>	<u>اد</u>	~	_ i	~	싛	~	
		ĸ		S	S	v	S		S	S	S	BamHI	į.	H			1	ez Total	<u>د</u> ان		ez trizi	5			
		4		G	b	G	G		۳	U		ä							0		زن	×	o	7	
		m		S	w	'n	S.		S	Ŋ	S					ω.			T ₂	Ī.		ű.		3	
		~		11	15					_	~					7		<u> </u>	Ų,	6	Š.	w.	un'	6	
1		-		~	~	~	~		~	z	ш		i i	3.0		_								1	
	9	•		S	۵	٧	-	1	۵	S	۵.				TO.					ě.		√7 • z	9		
		8	ĕ	۵ >	_	۵.	-		>	>	-			1000	_	6		>	اُند		¥.	Ĵ.	ž	4	
	}	7	SanDI	5	0	9	0	1	Γō	-6	g	1	ŀ					2	2	٤,	\$		12	۵	
5:		9		8	, vi	i.		137	5		. w	Bsu361				7				¥.		2	1	1	
CDR.1		2		o			113	3	a		o.	8	- [8		9		-	Ö	٥	Ö,	ui.	Ġ.	Ş.	
		4			2		ú	S	<u>ح</u>	-	4.2		ļ	Ö		S.		Ű	ψ.	۵	G	Ű,	ø.	Š	
2		'n		va	Ľ	to	\mathbb{R}_2		Ó	<u>.</u>	٩		ľ			4		Œ	in	a.	U,	λó	Þ	¥	
8		~		S	vı	v	ູ້ທ		=	ui	Ü		į.			e		Ξ.	z.	ż	YX.	٠.	فا	yr.	
	١.	-		1	B	734	14	4	3		'n		l			ບ			١.,	3			3		
	٦,	0			4	ť	· 3		4	ė	۵		Į.			٩		. 6	1,5	9	Ċ.		7	4	
-	1	6		>	<u>~</u>	>	>	-	>	>	>	•				æ		iL.	ايو	e.	ų	1.1	0		
	1	8	ធ	-	Н	50-1	-	1	=	-	-			ANY CAME		7		4	Z.	۵	s,				
		7	Asei	_	Ļ	ب	_		_	Σ	>			5		-			4	Ŧ					
		9			د	_	د	•	-	د	ب		Ł		2	0		œ,	,		Š	(/)	-	¥.	
1		ß		¥	0	~	¥		_×	¥	>					6		b	U	٧	S	9	g	ŋ	
12	1	4		۰	۵	۵.	_		۵.	Р	٥.	Bbei	i			8		Σ	Σ	_	>	-	Σ	_	
ž	1	m		4	S	4	-		⋖	<	<	#	ļ			7		_ ≥	≱	3	3	3	>	3	
18	ĺ	~		×	o	0	0		۲	×	0		i			9	Xhoĭ	ш	ш	ш	ш	ш	ш	w	
Framework 2			SexAI	ि	U	ď	G		9	ט	9	۱.,	ļ	~		ı	×	느	_	_	_				
1=	4	0	S	٥	۵	٥	۵	_	۵	Δ.	Δ.	Ē		Framework 2		4		Ģ	O	4	9	9	Ü	ن	
		6		¥	¥				ر.	Ξ	¥			Š.	l	m		٥	0	<u>×</u>	×	<u>×</u>	<u>×</u>	~	ı
		8		0					0					Ë		7		۳	ט	9	9	9	ט	9	
	1	7		٥		<u> </u>		_	۴			7	1	E	ĺ	-	BSECT	4	•	۵.	۵.	_	4	ь.	
		9	Koni	/	>	>	>	1	≻	>	>	ē			4	0	8	۲	۷.	۵.	۷.	<u>.</u>	Σ~	2	
1	Ì	ĸ	₹	∖≥	₹	3	: ≥	1	≥	₹	≥	۱×	1		l	6		0	0	0	ď	0	0	O	i



Sequence Summary HuCAL Libraries scFv1, scFv2, scFv3 and Fab1

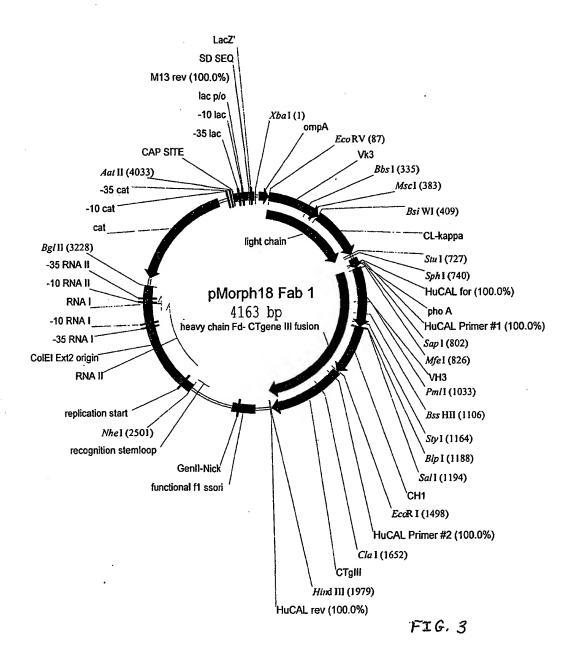
7	Framework 1
Position	4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 a b c d e f 1 2 3 4 5
	Koni
VLK1	COT OTIO ACC ATT ACC TOC. WAS SOCIETED ON SOCIATIVACIANCE ACCURATION OF THE TOTAL OTION OTION OF THE TOTAL OTION
	OTTO ALCE OTTO OTTO BOTH OF OTTO GOAD AND AND THE HAMP AGGINET COMMANDE CITIE OF THE CAME AND CONTINUABLE AND THE SHE WAS THE THE SHE WAS THE
VLG	on oos eas ean oon oos nos cre nos nos resignados estados estados en entra en estados en estados en estados en estados en entra en estados en entra en estados en entra en entra entra en entra en entra en entra entra en entra
	GAT ATC GITC ATTO AND ACC COS GAT AGC CTO GGG GTO AGC CTO GGG GAA CGT GGG AGC ATT AAC TICC/AGC MAC ANG CAS GTG ATTO AGC AGG AGC AGG AGG AGG AGG AGG AGG AGG
יייי	TCA GTG AGT GGC GGA CCA GGT OAG CGT GTG ACC ATC TCG TGT AGG 1960,
	TO SITE ASS SEC THA COA SOOT LAS ASS ATT ASS APE TOS THE NOS SOOT SECTION SECT
VLX3	GAT ATC GAA CTG ACC CAG COC CCT . TOA GTO ACC GTO TOA ACC GOOD GOT ATC TOO TIET TO TIET TO TIET TO TIET TO THE TOA THE
ı	FEDRY Sev-AI BISSSI KPIII KPIII
H	
L _	Framework 1 Framework 1
j :	1 2 9
Position	7 8 9 0 1 a b 2 3 4 5 6 7 8 9
	Mei
	THE ALL MATTERS AND THE CITE COLD CAN GOD
	GIRG CAN THE GITT CAG AGG GGG GGG GGG GGG AGG GGG GGG AGG GTG AAA GTG AGG TGG AAA GGC TGG AAA GGC TGG GGG GGG GGG GGG GGG GGG GGG GGG
	THE CAN THE LAM AGE GGC CCC GCC GCC GCC GCC GCC GCC GCC G
	GITS CAN TITE GITS GAN AGE GGC GGC GGG GGG CAG GGG GGC AGC CTG GGT CGG AGC TGC GGG GGC TGC GGAN TITT AGC TITE AGG AGG TGC GAN AGC TGC CAN GGC
	COS GGC CTG GTG AAA COS AGC GAA ACC CTG AGC CTG ACC TGC ACC GTT TO GGA BGC AGG ATT ACC AGG AGC AGG AGG
VHS	CA TTG GIT CAG ACC GCG GCA GTG AAA AAA CCG GCA ACC CTG AAA ATT AGC TGC AAA GGT TCC GCAA GGT TCC GCAA ACC CTG AAA ATT ACC TGC AAA GGT TCC GCAA ACC CTG AAA ATT ACC TGC AAA ATT ACC TGC AAA ATT ACC TGC AAA ATT CCT AAAA ATT CCT AAAA ATT CCT AAAA ATT CCT AAAAA ATT CCT AAAAAA ATT CCT AAAAAAA ATT CCT AAAAAAAA
	GTG CAA TTG CAA CAG TCT GGT COG GGC CTG GTG AAA COG AAC CAA ACC CTG ACC TGT GAC TTG TCH CAA CAG TCT GGT COG GGC CTG GTG AAA COG AAC CAA ACC CTG ACC TGT ACC TG
	T/6.7

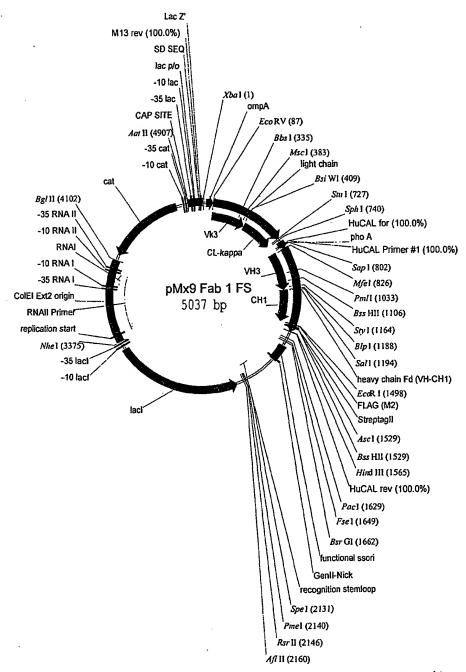
Framework 2	Framework 3
4	K 6 7 8
9 0 1 2 3 4 5 6 7 8	9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4
Sexal Asel	
AND CCA GGT AND GCA CCG AND CITA TTA ATT	THE GOLD WITH THE CONTINUE CON
AND CCA GGT CAA AGC CCG CAG CTA TTA ATTT T	GAT CET TIT AGE GGE TET GGA TEC GGE ACE GAT TIT ACE CTG AAA ATT AGE CGT GTG GAA GAT GAA GAL GIG
AN COA GGT COA GCA COG CGT COA TTA ANT 1	CCS GCG CGT TITT AGC GGC TCT GGA TCC GGC ACG GAT TITT ACC CTG ACC
AND COA GOTT CAG COG COG ANA CITA TITA ATIT T	ATTENDED FOR THE MEDIAGE GIT COS OUT COT TIT AGG GCC TOT GGA TOO GGC ACT GAT TIT ACT CIN ACT ALI IND INC. CIN CAN UNITED WAS A TO GGC TOT GGA TOO GGC ACT GAT TIT ACT CIN ACT ALI IND INC. CIN CAN UNITED WAS A TO GGC TO G
	THE STATE OF THE S
TIG CCC GGG ANG GGG CGG ANA CTG ATTE ATT	THE PART AND THE COURT OF THE COURT OF THE PART OF THE
AAA CCC GGG CAS GGG CCA GTT CTG GTG ATT	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
, was	
work 2	Framework 3
20	9
3 4 5 6 7 8 9 0 1 2	a b c 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 a b c
g	BSEEL NSDV
CAG GGT CTC GAG TGG ATG GGC GGC ATT ALT	TO THE STATE SHEET SECTIONS SATE WITH STATE SHEET SHEE
	TOTAL THE COCCUSION WITH THE GOSTON AND THE CONSTITUTION OF THE MED ATTO ACC COST ON THE COST TAT ATTO GOAD THE MAC ACC TOTAL THE COST TAT ATTO GOAD THE WAS THE
	Too. ONT GATE SATE AND THE THE ACC ACC ACC COT CO ACC ATT ACC ANT ACT TOO AND ANT CAG GTS GTG CTG ACT ATG ACC ANG ATT
	COT GAT ANT TOG AND ANC ACC CTG TAT CTG CAA ATG ANC AGC
AMG GET CITC GAG TIGG ATT GGC TAT ATT THE	ACT TOG AND AND CAG TIT AGO CTG ANA
ANG GGT CTC GAG TGG ATG GGC ADT ATT TAT	
ट्या उद्धाटाट दम्हा पदं टाव उद्धावन मुद्दा मु	TRECEGUES AND SECURITIES OF SHELLING SECURITIES OF SHELLING SHELLI

716.7, cart.

																. •	٠	¥ -	*-	ব-	₩-	-	\	₽		
																-		Ē	5	Ē	ь	Ę	Ę	E		
															=	0		ষ্	ğ	ğ	ğ	STG ACG	GTG ACG	GTG ACG		
														4		6		35	100	Ę	Ę	E	313	316		
														NO.		8		CTG GTG ACG	टाड डाड बट्ड डार	2	टाड डाड ४०६ डार	200	g	g		1
														Framework 4				ğ	υ μ	ACC CTG GTG ACG	S S	Å	Agg	ξ Q		
														Ŧ		_			g Ag		Ä		υ ¥			
																9	-	95 ₹3	8	g	8	8	ष्ठ	8		
																'n	हे		₹	₹	₹	₹	₹	8		
																4	,	병	넁	병	병	병	병	쏂		
																e		8	8	9	100	166	图	55		
																2			9	×		1				
																_		Į.	包	Œ	J.					
																		9	or,		ď	5	3			
			-													_		1.		Ę			34	6		
		o ;	₃ 3	ğ	ğ	ğ	ğ	ſ	8	3	ទី]					-		*	*	7		*	Ų.	***		
		ω i	BSW	8	ह	B	8	İ	မွ	9	<u>ဒ</u>	3		B		_		8	3	ıε	8	8	3	8		
		^	- 1	<u> </u>	<u>¥</u> ₹	<u>₹</u>	\$	L	É	É	Į					6		3	8	8	Š	3	8			
11				¥	A TA	¥±	H		E	E	Ē					Ļ		¥	Ś	Ź	Ė	¥	4			
		w .		Z	Æ	<u>ح</u>	₽ V			E								Z	Š				2			
		ru.		≸	₹	§	8		å	¥	S	_		3		Ð			Č	×				3		
4		4		5	Ē	E	Ę	-	Ê	Ê	Ĕ	큠		2		0		3	ž	Z	8	Ť	Ť	9		
퉏		m		≨	≨	₹	≸	ı	¥	뙇	뜋	ı		8		v		3	3	:8	ε	3	Ξ	8		
new		~		ACG AVA	g	ğ	ğ		8	8	8					۵		8	8	. 2	E	8	8	8		
Framework 4		_		٩ ووا	GGT ACG AAA	وا ۴	GGT A		GGC GGC GGC ACG ANG TTA ACC	TIT GGC GGC GGC ADG ANG TTA	GGC GGC ACG AMG TTA ACC					ra		2		8	£	.ε		8		
1	_	_		წ ღ	ც ი		ც ი		ğ	ñ	ğ			3	٠	_		ě	3	÷	· S	\o				
	2	•	_[8	Š	8	8		9	8	g				-	٠		9	-	. 9	1		Œ.			
	i	σ.		ပ္ပ	g	မ္မ	g		ğ	ğ	9					6		×		<u>.</u> 4	×	×				
		œ	L	E	F -	F	븨		E	E	E					8		8	¥	8	Z	8	â	8		
		^		ខ្ន	ă	Ą	ğ		g	96	GTG					^		.3	8	,8	渇	8	S	8		
77.		w	į,	-				1	. *1			ı				9			8	2		38		8		
		_			4.	19	4.			塔						ın					搜		13			
7.7		Δ					7.7			9				37	1	_		阜	(2) -	3 (E	- -:	MEE J.	经投 :-[5003.i =	1	
-		10							8	3	8					4	Ħ	L	- 13	-8	. 13	- 13	- 13	U		
1		ιυ			Š.	×		15	Α,		·	1		-		m	BSSHI	윊		8	g	8	g	8		
8		4			.	/ x /	8				*					7	,	ſβ	မှု	말	_날	용	별	မ	l	
S.		m		4				2	36							-		ΤĀΤ	TAT	¥	ŦĀ	TAT	ΤĀ	Ħ		
		2			ì			× 4		H	b				6		,	TAT					¥	Ā		
X		•	h	ţ	1.4			1	و.	2	Q S				1	c.		_ 2				<u> </u>	ץ שני	- B		
		-			7	×.		W	Ų.	T.				1	1		7	وا	υ] ₹	L ₀	ы Н	٦ پر	N N		
3	6	0	ŀ	ð	ថ្ម	ថ	Š	0	H	Ľ	F			-	1	œ	Eag	50	AG 600 GHG	AG GC	8	35	8	မွ		
		σ		×	*	×	*		8	8	8	1			-	,	•			ηğ					ì	
	1	ω,	٠	둳	β	ष्ट	얼		뀰	ğ	ß					٠	•	AT.	8	GTG GAT	GAA GAT	PA PA	Ą	GAA GAT		
		^		TAT	TAT		TAT		TAT	TĀT.	TAT					Ľ	•	AGC GAA GAT	GAA GAT	6	8	GCG GAT	Ą	3		
		9		TAT	TAT	CIT TAT TAT	TAT		TAT	TAT	TAT					4		٢	ÿ	8	8	g	g	8		
-	1		Ę	į		Ē	1							1												
ļ		Ŋ		5	B	Ę	9		Æ	B	Ą					~	•	į	9	GAC	5	å	AA	Â		
1			į	₹		-4	3							ı	1											

The 2 cmt.





FIG, 4

50	20	
1 CICYPPHPOIDAFCNSDLVIRAKEVGTPBVNOTILYORYEIKMIKMYKGFO 50	TAFCNSDLVIRAKFMGSPEIIETTLYQRYEIKMTKMLKGFD	水水水 水水水水水水水水水水水水水 水水 水 水水水水水水水水水水水水水水水
TIMP1 human 135850	TIMP1_rat 1174697	

TIMP1_human 135850 TIMP1_rat 1174697

TIMP1_human 135850 TIMP1_rat 1174697

LLOGSEKGFOSRHLACLPREPGLCTWQSLRSQIA
ILMGSEKGYQSDHFACLPRNPDLCTWQYLGVSMTRSLPLAKAEA 194
.* *****,** * ***** * ***** * ... 151 TIMP1_human 135850 TIMP1_rat 1174697

FIG. 5

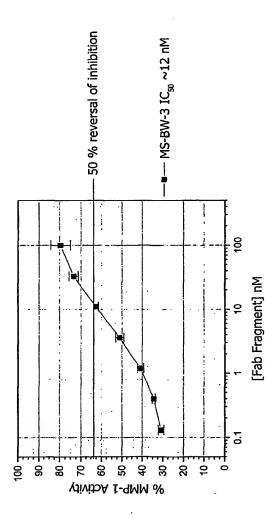


FIG. 6

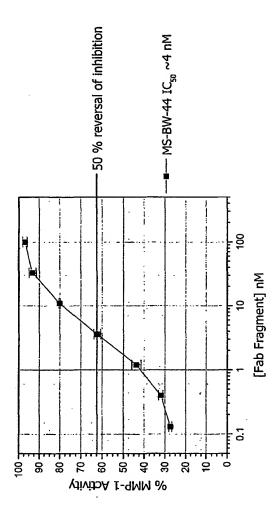


FIG.

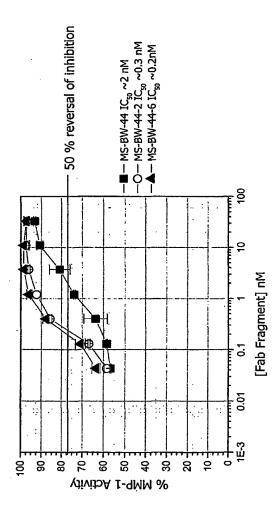


FIG. 8

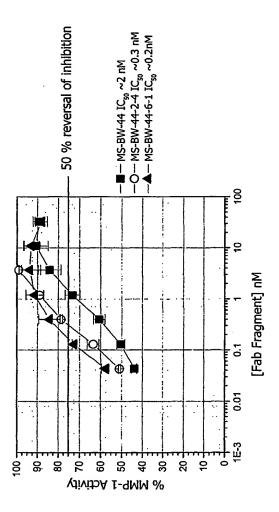


FIG. 9

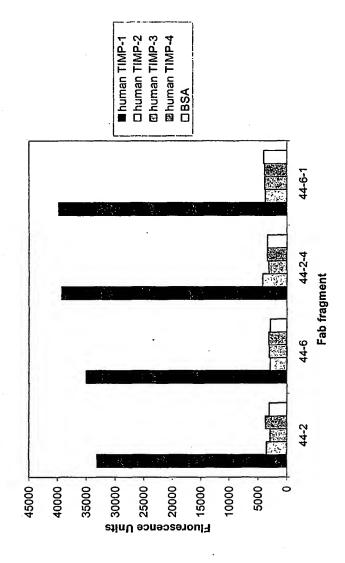


FIG. 1

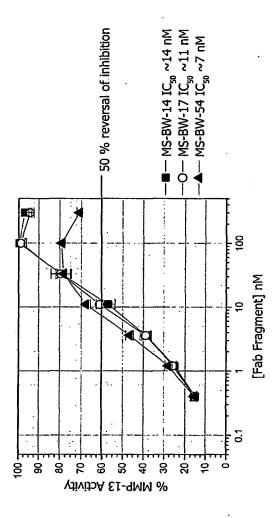


FIG. 11

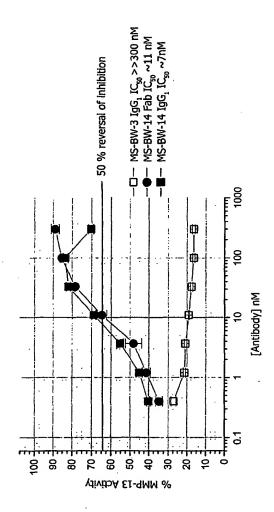


FIG. 12

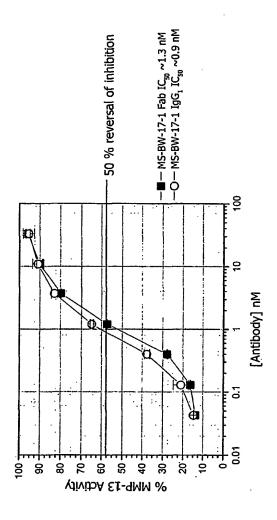


FIG. 13

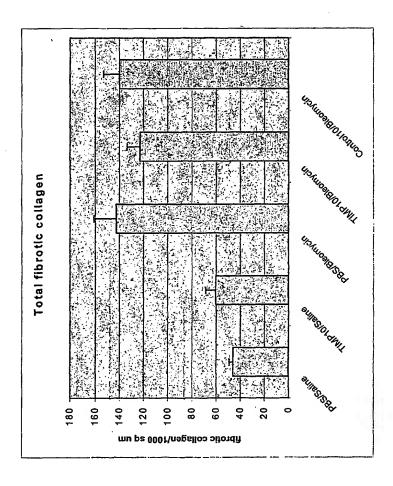


FIG. 14

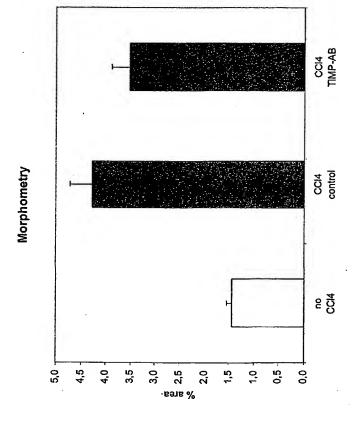


FIG. 1

SEQUENCE LISTING

```
<110> Bayer Corporation
      MorphoSys AG
<120> Human TIMP-1 Antibodies
<130> 02973.00074
<150> US 60/285,683
<151> 2001-04-24
<160> 381
<170> FastSEQ for Windows Version 4.0
<210> 1
<211> 4
<212> PRT
<213> Homo sapiens
<400> 1
Phe Met Asp Ile
1
<210> 2
<211> 4
<212> PRT
<213> Homo sapiens
<400> 2
Gly Phe Asp Tyr
1
<210> 3
<211> 4
<212> PRT
<213> Homo sapiens
<400> 3
Phe Leu Asp Ile
1
<210> 4
<211> 8
<212> PRT
<213> Homo sapiens
```

```
<400> 4
Thr Phe Pro Ile Asp Ala Asp Ser
<210> 5
<211> 5
<212> PRT
<213> Homo sapiens
<400> 5
Gly His Val Asp Tyr
<210> 6
<211> 9
<212> PRT
<213> Homo sapiens
<400> 6
Tyr Trp Arg Gly Leu Ser Phe Asp Ile
<210> 7
<211> 4
<212> PRT
<213> Homo sapiens
<400> 7
Phe Phe Asp Tyr
<210> 8
<211> 12
<212> PRT
<213> Homo sapiens
Gly Leu Tyr Trp Ala Val Tyr Pro Tyr Phe Asp Phe
<210> 9
<211> 11
<212> PRT
<213> Homo sapiens
Leu Asp Thr Tyr Tyr Pro Asp Leu Phe Asp Tyr
<210> 10
```

```
<211> 7
<212> PRT
<213> Homo sapiens
<400> 10
Thr Tyr Tyr Tyr Phe Asp Ser
<210> 11
<211> 11
<212> PRT
<213> Homo sapiens
<400> 11
Tyr Met Ala Tyr Met Ala Glu Ala Ile Asp Val
<210> 12
<211> 17
<212> PRT
<213> Homo sapiens
<400> 12
Leu Val Gly Ile Val Gly Tyr Lys Pro Asp Glu Leu Leu Tyr Phe Asp
1
Val
<210> 13
<211> 9
<212> PRT
<213> Homo sapiens
<400> 13
Tyr Gly Ala Tyr Phe Gly Leu Asp Tyr
<210> 14
<211> 9
<212> PRT
<213> Homo sapiens
<400> 14
Gly Tyr Ala Asp Ile Ser Phe Asp Tyr
<210> 15
<211> 7
<212> PRT
<213> Homo sapiens
```

```
<400> 15
Tyr Tyr Leu Leu Leu Asp Tyr
<210> 16
<211> 16
<212> PRT
<213> Homo sapiens
Trp Ser Asp Gln Ser Tyr His Tyr Tyr Trp His Pro Tyr Phe Asp Val
<210> 17
<211> 7
<212> PRT
<213> Homo sapiens
<400> 17
Leu Ile Gly Tyr Phe Asp Leu
<210> 18
<211> 12
<212> PRT
<213> Homo sapiens
<400> 18.
Leu Thr Asn Tyr Phe Asp Ser Ile Tyr Tyr Asp His
<210> 19
<211> 12
<212> PRT
<213> Homo sapiens
<400> 19
Leu Val Gly Gly Tyr Asp Leu Met Phe Asp Ser
<210> 20
<211> 13
<212> PRT
<213> Homo sapiens
<400> 20
Tyr Val Thr Tyr Gly Tyr Asp Asp Tyr His Phe Asp Tyr
```

```
<210> 21
<211> 6
<212> PRT
<213> Homo sapiens'
<400> 21
Ser Gly Tyr Leu Asp Tyr
<210> 22
<211> 18
<212> PRT
<213> Homo sapiens
Tyr Ile Gly Tyr Thr Asn Val Met Asp Ile Arg Pro Gly Tyr Phe Leu
Asp Tyr
<210> 23
<211> 12
<212> PRT
<213> Homo sapiens
<400> 23
Phe Arg Ala Tyr Gly Asp Asp Phe Tyr Phe Asp Val
                 5
<210> 24
<211> 15
<212> PRT
<213> Homo sapiens
<220>
<221> VARIANT
<222> (1)...(15)
<223> Xaa = Any Amino Acid
Xaa Met Trp Ser Asp Tyr Gly Gln Leu Val Lys Gly Gly Asp Ile
<210> 25
<211> 11
<212> PRT
<213> Homo sapiens
<400> 25
Tyr Tyr Val Thr Asp Thr Ala Tyr Phe Asp Tyr
```

```
. 10
<210> 26
<211> 11
<212> PRT
<213> Homo sapiens
<400> 26
His Asp Phe Asp Gly Ser Ile Phe Met Asp Phe
1 5
<210> 27
<211> 12
<212> PRT
<213> Homo sapiens
<400> 27
Tyr Ala Gly His Gln Tyr Glu Phe Phe Asp Phe
           5
<210> 28
<211> 11
<212> PRT
<213> Homo sapiens
<400> 28
Leu Tyr Ala Asp Ala Asp Ile Tyr Phe Asp Tyr
               5
                                  10
<210> 29
<211> 9
<212> PRT
<213> Homo sapiens
<400> 29
Thr Lys Tyr Val Gly Ser Glu Asp Val
<210> 30
<211> 9
<212> PRT
<213> Homo sapiens
<400> 30
Tyr Arg Tyr Pro His Met Phe Asp Phe
<210> 31
<211> 11
<212> PRT
```

```
<213> Homo sapiens
<400> 31
Leu Phe Ala Gly Leu Glu Leu Tyr Phe Asp Tyr
<210> 32
<211> 8
<212> PRT
<213> Homo sapiens
<400> 32
Gly Gly Phe Phe Asn Met Asp Tyr
<210> 33
<211> 10
<212> PRT
<213> Homo sapiens
<400> 33
Gly Tyr Ile Pro Tyr His Leu Phe Asp Tyr
<210> 34
<211> 12
<212> PRT
<213> Homo sapiens
<400> 34
Tyr Tyr Gly Phe Glu Tyr Asp Leu Leu Phe Asp Asn
<210> 35
<211> 8
<212> PRT
<213> Homo sapiens
<400> 35
Ile Thr Tyr Ile Gly Tyr Asp Phe
<210> 36
<211> 7
<212> PRT
<213> Homo sapiens
<400> 36
Gln Glu Trp Tyr Met Asp Tyr
```

```
<210> 37
<211> 11
<212> PRT
<213> Homo sapiens
<400> 37
Leu Tyr Pro Glu Asp Leu Ile Tyr Phe Asp Tyr
<210> 38
<211> 15
<212> PRT
<213> Homo sapiens
<400> 38
Trp Met Thr Pro Pro Gly His Tyr Tyr Gly Tyr Thr Phe Asp Val
<210> 39
<211> 12
<212> PRT
<213> Homo sapiens
<400> 39
Leu Arg Val His Asp Tyr Ala Met Tyr Phe Asp Leu
<210> 40
<211> 13
<212> PRT
<213> Homo sapiens
Phe Val Ser Tyr Asn Gly Ser Val Pro Tyr Phe Asp Tyr
<210> 41
<211> 11
<212> PRT
<213> Homo sapiens
<400> 41
Ile Ile Gly Asp Tyr Val Ile Phe Phe Asp Val
<210> 42
<211> 11
<212> PRT
<213> Homo sapiens
```

```
<400> 42
Leu Phe Thr Tyr Pro Phe Leu Tyr Phe Asp Val
<210> 43
<211> 11
<212> PRT
<213> Homo sapiens
<400> 43
Ile Leu Thr Gly His Val Leu Leu Phe Asp Tyr
               5
<210> 44
<211> 9
<212> PRT
<213> Homo sapiens
<400> 44
Gln Ser Tyr Asp Tyr Gln Gln Phe Thr
                5
<210> 45
<211> 9
<212> PRT
<213> Homo sapiens
<400> 45
Gln Ser Tyr Asp Phe Lys Thr Tyr Leu
<210> 46
<211> 9
<212> PRT
<213> Homo sapiens
Gln Ser Tyr Asp Phe Leu Arg Phe Ser
<210> 47
<211> 9
<212> PRT
<213> Homo sapiens
<400> 47
Gln Ser Tyr Asp Phe Ile Asn Val Ile
```

```
<210> 48
 <211> 9
 <212> PRT
 <213> Homo sapiens
 <400> 48
 Gln Ser Tyr Asp Phe Val Arg Phe Met
 <210> 49
 <211> 9
 <212> PRT
 <213> Homo sapiens
. <400> 49
 Gln Ser Tyr Asp Phe Tyr Lys Phe Asn
 <210> 50
 <211> 9
 <212> PRT
 <213> Homo sapiens
 <400> 50
 Gln Ser Tyr Asp Phe Arg Arg Phe Ser
 <210> 51
 <211> 9 .
 <212> PRT
 <213> Homo sapiens
 <400> 51
 Gln Ser Arg Asp Phe Asn Arg Gly Pro
 <210> 52 ·
 <211> 8
 <212> PRT
 <213> Homo sapiens
 Gln Ser Tyr Asp Gln Arg Lys Trp
  1
 <210> 53
 <211> 8
 <212> PRT
 <213> Homo sapiens
```

```
<400> 53
Gln Gln Leu Tyr Gly Thr Val Ser
<210> 54
<211> 9
<212> PRT
<213> Homo sapiens
<400> 54
Gln Ser Tyr Asp Gly Phe Lys Thr His
<210> 55
<211> 8
<212> PRT
<213> Homo sapiens
<400> 55
Gln Ser Tyr Asp Tyr Ser Leu Leu
<210> 56
<211> 8
<212> PRT
<213> Homo sapiens
<400> 56
Gln Ser Tyr Asp Phe Asn Phe His
<210> 57
<211> 10
<212> PRT
<213> Homo sapiens
<400> 57
Gln Ser Tyr Asp Met Ile Ala Arg Tyr Pro
<210> 58
<211> 10
<212> PRT
<213> Homo sapiens
Gln Ser Trp Asp Ile His Pro Phe Asp Val
<210> 59
```

```
<211> 8
<212> PRT
<213> Homo sapiens
<400> 59
Gln Ser Trp Asp Leu Glu Pro Tyr
<210> 60
<211> 9
<212> PRT
<213> Homo sapiens
<400> 60
Gln Ser Tyr Asp Val Leu Asp Ser Glu
<210> 61
<211> 10
<212> PRT
<213> Homo sapiens
<400> 61
Gln Ser Tyr Asp Pro Ser His Pro Ser Lys
           5
<210> 62
<211> 8
<212> PRT
<213> Homo sapiens
<400> 62
Gln Ser Tyr Asp Asp Met Gln Phe
                5
<210> 63
<211> 9
<212> PRT
<213> Homo sapiens
<400> 63
Gln Ser Trp Asp Ile Asn His Ala Ile
<210> 64
<211> 9
<212> PRT
<213> Homo sapiens
<400> 64
```

```
Gln Ser Tyr Asp Tyr Tyr Asp Tyr Gly
<210> 65
<211> 8
<212> PRT
<213> Homo sapiens
<400> 65
Gln Gln Ala Asn Asp Phe Pro Ile
<210> 66
<211> 10
<212> PRT
<213> Homo sapiens
<400> 66
Gln Ser Trp Asp Asn Leu Lys Met Pro Val
<210> 67
<211> 10
<212> PRT
<213> Homo sapiens
<400> 67
Gln Ser Tyr Asp Val Phe Pro Ile Asn Arg
<210> 68
<211> 7
<212> PRT
<213> Homo sapiens
<400> 68
Gln Ser Asp Leu Tyr Phe Pro
<210> 69
<211> 8
<212> PRT
<213> Homo sapiens
<400> 69
Gln Ser Tyr Asp Val Thr Pro Arg
<210> 70
<211> 9
```

```
<212> PRT
<213> Homo sapiens
<400> 70
Gln Ser Tyr Asp Pro Val Gly Phe Pro
<210> 71
<211> 8
<212> PRT
<213> Homo sapiens
<400> 71
Gln Ser Tyr Asp Leu Ser Pro Arg
                5
<210> 72
<211> 10
<212> PRT
<213> Homo sapiens
<400> 72
Gln Ser Tyr Asp Phe Ser His Tyr Phe Phe
                5
<210> 73
<211> 9
<212> PRT
<213> Homo sapiens
<400> 73
Gln Ser Tyr Asp Leu Arg Tyr Ser His
<210> 74
<211> 8
<212> PRT
<213> Homo sapiens
Gln Ser Tyr Asp Leu Arg Asn Arg
<210> 75
<211> 9
<212> PRT
<213> Homo sapiens
<400> 75
Gln Ser Tyr Asp Phe Thr Tyr Gly Ser
```

```
1
<210> 76
<211> 8
<212> PRT
<213> Homo sapiens
<400> 76
Gln Gln Phe Asn Asp Ser Pro Tyr
<210> 77
<211> 9
<212> PRT
<213> Homo sapiens
<400> 77
Gln Ser Tyr Asp Ile Ser Gly Tyr Pro
          5
<210> 78
<211> 10
<212> PRT
<213> Homo sapiens .
<400> 78
Gln Ser Arg Asp Leu Tyr Tyr Val Tyr Tyr
               5
<210> 79
<211> 8
<212> PRT
<213> Homo sapiens
<400> 79
Gln Ser Tyr Asp Arg Ser Met Trp
<210> 80
<211> 9
<212> PRT
<213> Homo sapiens
<400> 80
Gln Ser Trp Asp Val Gln Thr Asp Lys
                5
<210> 81
<211> 9
<212> PRT
```

```
<213> Homo sapiens
<400> 81
Gln Ser Trp Asp Pro Ser His Tyr Tyr
            5
<210> 82
<211> 9
<212> PRT
<213> Homo sapiens
<400> 82
Gln Ser Tyr Asp Ile Met Pro Glu Arg
1 5
<210> 83
<211> 9
<212> PRT
<213> Homo sapiens
<400> 83
Gln Ser Met Asp Phe Arg Leu Met His
1 5
<210> 84
<211> 9
<212> PRT
<213> Homo sapiens
<400> 84
Gln Ser Phe Asp Met Ile His Pro Tyr
<210> 85
<211> 7
<212> PRT
<213> Homo sapiens
<400> 85
Gln Ser Asp Phe Pro Val Met
1 5
<210> 86
<211> 7
<212> PRT
<213> Homo sapiens
<400> 86
Gln Ser Asp Asn Pro Tyr Leu
```

```
<210> 87
<211> 11
<212> PRT
<213> Homo sapiens
<400> 87
Thr Cys Val Pro Pro His Pro Gln Thr Ala Phe
          5
<210> 88
<211> 12
<212> PRT
<213> Homo sapiens
<400> 88
Cys Thr Ser Val Pro Pro His Pro Gln Thr Ala Phe
               5
                                   10
<210> 89
<211> 12
<212> PRT
<213> Homo sapiens
<400> 89
Ser Thr Cys Val Pro Pro His Pro Gln Thr Ala Phe
               · 5
<210> 90
<211> 13
<212> PRT
<213> Homo sapiens
Ser Thr Ser Val Pro Pro His Pro Gln Thr Ala Phe Cys
               5
                                   10
<210> 91
<211> 10
<212> PRT
<213> Homo sapiens
<400> 91
Cys Glu Val Asn Gln Thr Thr Leu Tyr Gln
1 5
<210> 92
<211> 12
<212> PRT
<213> Homo sapiens
```

```
<400> 92
Pro Ala Met Glu Ser Val Cys Gly Tyr Phe His Arg
<210> 93
<211> 16
<212> PRT
<213> Homo sapiens
Pro Ala Met Glu Ser Val Cys Gly Tyr Phe His Arg Ser His Asn Arg
<210> 94
<211> 17
<212> PRT
<213> Homo sapiens
<400> 94
Cys Pro Ala Met Glu Ser Val Ser Gly Tyr Phe His Arg Ser His Asn
1
               5
                                  10
Arg
<210> 95
<211> 17
<212> PRT
<213> Homo sapiens
Pro Ala Met Glu Ser Val Ser Gly Tyr Phe His Arg Ser His Asn Arg
1 5
                                  10
Cys
<210> 96
<211> 12
<212> PRT
<213> Homo sapiens
Cys Leu Trp Thr Asp Gln Leu Leu Gln Gly Ser Glu
               5
<210> 97
<211> 215
<212> PRT
<213> Homo sapiens
```

```
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                                10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
        20
                             25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                         40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                     55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                          75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Gln
                               90
Gln Phe Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
                            105 110
         100
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
                       120
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                     135 . 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
                                    155
                  150
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
              165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
                 185 190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
   195
Thr Val Ala Pro Thr Glu Ala
 210 .
<210> 98
<211> 215
<212> PRT
<213> Homo sapiens
<400> 98
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                                 10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
                             25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                         40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                     5.5
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                 70
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Lys
                                90
Thr Tyr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
```

```
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    115
           120
                             125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                    135
                                    140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
     150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            165
                 170
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
                 185
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
              200
Thr Val Ala Pro Thr Glu Ala
<210> 99
<211> 211
<212> PRT
<213> Homo sapiens
<400> 99
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                              10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
          20
                           25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                       40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                    55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                70
                                 75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Leu
             85
                              90
Arg Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
         100
                          105
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
                       120
                                         125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                    135
                                    140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
              150
                        155
Ala Gly Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
       165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
      180 185
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
                       200
Thr Val Ala
```

210

```
<210> 100
<211> 215
<212> PRT
<213> Homo sapiens
<400> 100
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5
                  10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                      40
                                       45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
          55
                              60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                     75
      70
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Ile
  85
                             90
Asn Val Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
                          105
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120
                                        125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                    135
                                  140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            165 170
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
                       200
Thr Val Ala Pro Thr Glu Ala
<210> 101
<211> 215
<212> PRT
<213> Homo sapiens
<400> 101
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
             5
                        10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
   20
                           25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                       40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                   55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
```

```
70
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Val
Arg Phe Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
                           105
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
                               125
                       120
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                    135
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
                       155
       150
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
       165 170
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
      180 185
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 · 200
Thr Val Ala Pro Thr Glu Ala
 210
<210> 102
<211> 215
<212> PRT
<213> Homo sapiens
<400> 102
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
                           25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                        40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                    55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Tyr
                               90
Lys Phe Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
                           105
          100
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
                        120
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                    135
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
                150
                         155
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
             165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
```

185

```
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195
          200
Thr Val Ala Pro Thr Glu Ala
 210
<210> 103
<211> 215
<212> PRT
<213> Homo sapiens
<400> 103
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                              10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
                          25
 20
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                     40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                 55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
              70
                                  75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Arg
                              90
Arg Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
                                          110
          100
                           105
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
      115
                       120
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                    135
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
               150
                                 155
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            165 170 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
        180 185
                                           190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200
Thr Val Ala Pro Thr Glu Ala
 210
<210> 104
<211> 214
<212> PRT
<213> Homo sapiens
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
                             10
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
```

```
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
                  70
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Phe Asn Arg
              85
                                 90
Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
                             105
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
                                     125
                         120
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
            135
                                140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
                                    155
145 150
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
             165
                                                     175
                                  170
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
       180
                              185
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
                          200
Val Ala Pro Thr Glu Ala
   210
<210> 105
<211> 213
<212> PRT
<213> Homo sapiens
<400> 105
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
                                 10
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
                              25
           20
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
                       55
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
                   70
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gln Arg Lys
                                  90
              85
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
```

140

105

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly

135

100

```
150
                                   155
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
           165
                          170
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
                            185
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
  195
                        200
Ala Pro Thr Glu Ala
  210
<210> 106
<211> 215
<212> PRT
<213> Homo sapiens
<400> 106
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
                                 10
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
                             25
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
                        40
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
                     55
                                      60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
                       . 75
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Tyr Gly Thr Ser
                                90
Val Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
                            105
         100
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
                      120
                                           125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
                     135
                                        140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
                 150
                                    155
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
           165 170
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
                          185
       180
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195
                         200
Ser Phe Asn Arg Gly Glu Ala
<210> 107
<211> 214
<212> PRT
<213> Homo sapiens
```

```
<400> 107
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
                                 10
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
                             25
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
                                  75
                  70
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gly Phe Lys
                                 90
             85
Thr His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
          100
                  105
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
                                             125
                         120
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
                      135
                                         140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
                   150
                                      155
Gly Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                                 170
               165
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
                             185 ·
           180
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
                          200
Val Ala Pro Thr Glu Ala
  210
<210> 108
<211> 211
<212> PRT
<213> Homo sapiens
<400> 108
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
                                  10
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
                              25
           20
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
                          40
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
```

55

85

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Ser Leu Leu Val 90

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala

75

```
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
 115
           120
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
                   135
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
                                 155
              150
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
                       170
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
                                 190
                 185
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
                        200 . 205
Thr Glu Ala
 210
<210> 109
<211> 211
<212> PRT
<213> Homo sapiens
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
                              10
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
                           25
 20
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35
                       40
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser 🔈
                  55
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
                                  75
                70
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Asn Phe His Val
             85
                              90
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
                        105
          100
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
                       120
                                         125
     115
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
                                  140
                    135
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
   150 155
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
                              170
          165
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
                          185 . 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
                        200
Thr Glu Ala
   210
```

```
<210> 110
<211> 216
<212> PRT
<213> Homo sapiens
<400> 110
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
                            25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
          40
                                         4.5
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                     55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
          <sub>,</sub> 70
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Met Ile
                               90
Ala Arg Tyr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
          100
                            105
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
      115 120
                            125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
                    135
                                     140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
               150
                                155
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
             165
                     170
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
         180 185 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
     195
                  200
Lys Thr Val Ala Pro Thr Glu Ala
210
<210> 111
<211> 213
<212> PRT
<213> Homo sapiens
<400> 111
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
  20
                           25
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35
                   40
                                      4.5
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
                    55
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
```

```
75
                  70
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ile His Pro Phe Asp
                               90
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
                            105
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
                        120
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
                    135
                              140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
       150
                         155
Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
      165
                     170
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
                           185
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
 195
Ala Pro Thr Glu Ala
  210
<210> 112
<211> 213
<212> PRT
<213> Homo sapiens
<400> 112
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
                           25
          20
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
                         40
Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
                     55
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
                  70
                                    75
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Leu Glu Pro
             85
                                90
Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
                            105
         100
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
                        120
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
                     135
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
                150
                                   155
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                      170
             165
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
```

```
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
   195
                    200
Ala Pro Thr Glu Ala
   210
<210> 113
<211> 215
<212> PRT
<213> Homo sapiens
<400> 113
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
              5 .
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
   20
                            25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                        40
                                           45
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                   55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                 70
                                    75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Leu
              85
                                90
Asp Ser Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
          100
                             105
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
                         120
                                           125
       115
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                     135
                                       140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
                150
                                   155
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
             165 170
                                         175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
       180 185
                                              190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200
Thr Val Ala Pro Thr Glu Ala
  210
<210> 114
<211> 216
<212> PRT
<213> Homo sapiens
<400> 114
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                               10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
```

```
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Pro Ser
                                  90
His Pro Ser Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
                              105
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
               120
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
             135
                                         140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
                150 155
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                                  170
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
                               185
                                                  190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
                           200
                                              205
Lys Thr Val Ala Pro Thr Glu Ala
    210
<210> 115
<211> 214
<212> PRT
<213> Homo sapiens
<400> 115
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                                  10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
                               25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
```

```
150
                               155
Gly Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
       165
                    170
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
         180 185 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
 195
                    200
Val Ala Pro Thr Glu Ala
 210
<210> 116
<211> 215
<212> PRT
<213> Homo sapiens
<400> 116
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20
                         25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                  55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
            70
                   75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ile Asn
                           90
His Ala Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
                        105
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
                     120
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                  135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
     150 155
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
           165 170
                                      175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
        180 . 185
                               190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205 .
Thr Val Ala Pro Thr Glu Ala
 210
<210> 117
<211> 215
<212> PRT
<213> Homo sapiens
```

```
<400> 117
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                       55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                  70
                                     75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Tyr
              85
                                  90
Asp Tyr Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
                             105
           100
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
                          120
                                             125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                      135
                                       140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
               150
                           155
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                                170 . 175
              165
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
         180
                              185
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
                           200
      195
Thr Val Ala Pro Thr Glu Ala
  210
<210> 118
<211> 215
<212> PRT
<213> Homo sapiens
<400> 118
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
                                  10
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
           20
                               25
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
                                      75
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ala Asn Asp Phe Pro
                                  90
Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
```

```
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
                        120
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
                    135
                                   140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
                                  155
                150
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                   170
    165
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
       180 185
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200
Ser Phe Asn Arg Gly Glu Ala
<210> 119
<211> 216
<212> PRT
<213> Homo sapiens
<400> 119
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                               10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
          20
                            25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                        40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                    55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                70
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Asn Leu
                               90
Lys Met Pro Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
                           105 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
                                         125
     115
                       120
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
                            · 140
                    135
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
                                   155
                150
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
             165
                               170
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
          180 185 190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
      195 200
Lys Thr Val-Ala Pro Thr Glu Ala
```

```
<210> 120
<211> 216
<212> PRT
<213> Homo sapiens
<400> 120
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                       10
1 5
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
                           25
20
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                       40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                          75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Phe
                             90
Pro Ile Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
  100 105
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
                   135
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
                 150
Lys Ala Gly Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
             165 170 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
  180 185
                                  190
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
                        200
Lys Thr Val Ala Pro Thr Glu Ala
<210> 121
<211> 213
<212> PRT
<213> Homo sapiens
<400> 121
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
              5
                               10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
          20
                           25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                       40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
```

55

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

```
70
                                      75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Leu Tyr Phe
                                  90
Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
                              105
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
                          120
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
                     135
                                         140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
        150
                           155
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
              165
                                 170
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
                    · 185
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
                          200
Ala Pro Thr Glu Ala
  210
<210> 122
<211> 214
<212> PRT
<213> Homo sapiens
<400> 122
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1
                                  10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
           20
                              25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                      55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                   70
                                     75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Val Thr
               85
                                  90
Pro Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
          100
                              105
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
                          120
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
                      135
                                          140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
                 150
                                     155
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
             165
                                 170
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
                              185
```

```
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
 195
                     200
Val Ala Pro Thr Glu Ala
  210
<210> 123
<211> 212
<212> PRT
<213> Homo sapiens
<400> 123
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
                             10
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
 20
                         25
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35
              40
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
                  55
                              . 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
                70
                                 75
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Pro Val Gly Phe Pro
            85
                             90
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
                105
         100
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
                       120
 115
                                       125
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
                   135
                                    140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
              150
                               155
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
            165
                             170
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
 180 185 190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
 195
             200
Pro Thr Glu Ala
 210
<210> 124
<211> 214
<212> PRT
<213> Homo sapiens
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                             10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
```

```
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Ser
                                90
Pro Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
       . 100
                          105
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
                        120
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
                     135
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
                                   155
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
          165 170
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
   180 185
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
                         200
Val Ala Pro Thr Glu Ala
   210
<210> 125
<211> 216
<212> PRT
```

<213> Homo sapiens

<400> 125

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln 10 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr 25 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu 35 ⋅ 40 4.5 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe . 55 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu 70 75 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Ser His Tyr Phe Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly 100 105 Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu 115 120 125 Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe 135 140 Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val

```
150
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
         165
                        170
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
                 185
                                  · 190
    180
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
 195 200
Lys Thr Val Ala Pro Thr Glu Ala
<210> 126
<211> 212
<212> PRT
<213> Homo sapiens
<400> 126
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
                 10 15
1 5
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
                           25
                                            30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
                       40
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
                                  75
65 70
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Arg Tyr Ser His
                 90
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
                 105 110
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
                      120
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
                   135
                                   140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150
                           155
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
                              170
            165
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
                          185
       180
                                    190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
 195
                       200
Pro Thr Glu Ala
 210
<210> 127
<211> 214
<212> PRT
<213> Homo sapiens
```

```
<400> 127
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
  1
                 5
                                     10
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
                                 25
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                         55
                                             60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                     70
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Leu Arg
                                    90
 Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100
                                105
                                                    110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
                            120
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
                        135
                                            140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
                   150
                                        155
Gly Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
               165
                                    170
                                                        175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
           180
                               185
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
     195
                           200
                                                205
Val Ala Pro Thr Glu Ala
   210
<210> 128
<211> 215
<212> PRT
<213> Homo sapiens
<400> 128
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                                    10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
                                25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                           40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                                           60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                   70
                                       75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Thr
                                   90
Tyr Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
```

105

```
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
           . 120
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                     135
                                      140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
              150
                                   155
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
             165
                     170
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
              185
   180
                                   190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
Thr Val Ala Pro Thr Glu Ala
<210> 129
<211> 215
<212> PRT
<213> Homo sapiens
<400> 129
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
                                10
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
                            25
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
                        40
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
                     55
                                       60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
                     . 75
                 70
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe Asn Asp Ser Pro
                                90
Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
                           105
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
                        120
                                           125
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
                    135
                                      140
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
                150
                                   155
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
             165
                               170
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
                            185
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200
Ser Phe Asn Arg Gly Glu Ala
```

```
<210> 130
<211> 215
<212> PRT
<213> Homo sapiens
<400> 130
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                        10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
          20
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                         40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                    55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
              70
                     75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ile Ser
                               90
Gly Tyr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
          100
                           105
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
                        120
                                          125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                    135
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            165 170
                                          175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
         180
                        185
                                             190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
   195
              200
Thr Val Ala Pro Thr Glu Ala
 210
<210> 131
<211> 216
<212> PRT
<213> Homo sapiens
<400> 131
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
          20
                            25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                       40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
```

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

```
70
                                     75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Arg Asp Leu Tyr
Tyr Val Tyr Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
          100
                             105
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
                        120
                                     125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
                     135
                                       140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
               150
                                   155
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
             165
                       170
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
                   185
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
              200
Lys Thr Val Ala Pro Thr Glu Ala
 210
<210> 132
<211> 211
<212> PRT
<213> Homo sapiens
<400> 132
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
                   10
1 5
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
                    25
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser.
                     55
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
                 70
                                    75
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg Ser Met Trp Val
                                 90
              85
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
          100
                            105
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
                         120
                                            125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
                     135
                                       140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
                                    155
                 150
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
                               170
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
                             185
```

```
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
                         200
Thr Glu Ala
  210
<210> 133
<211> 215
<212> PRT
<213> Homo sapiens
<400> 133
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                                7.0
              5
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
                             25
 20
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                        40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                      55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                  70
                                    75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Val Gln
                                90
              85
Thr Asp Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
          100
                            105
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu.
                        120
                                           125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                     135
                                       140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
                 150
                                   155
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
           165 170
                                                  175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
                   185
          180
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
               200
    195
                                          205
Thr Val Ala Pro Thr Glu Ala
 210
<210> 134
<211> 212
<212> PRT
<213> Homo sapiens
<400> 134
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
                               10
       5
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
                             25
```

```
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Pro Ser His Tyr Tyr
                               90
              85
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
          100
                           105
Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
                         120
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
                     135
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
                 150
                                   155
Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
             165
                         170
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
       180
                             185
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
Pro Thr Glu Ala
   210
<210> 135
<211> 215
<212> PRT
<213> Homo sapiens
<400> 135
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
               5.
                                  10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
          20
                              25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                          40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                   70
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ile Met
              85
                                  90
Pro Glu Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
                              105
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
                         120
                                             125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
```

135

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys

```
155
               150
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                   170
         165
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
                185
         180
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195
             200
Thr Val Ala Pro Thr Glu Ala
 210
<210> 136
<211> 215
<212> PRT
<213> Homo sapiens
<400> 136
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5
                 10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
                          25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                   75
     70
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Met Asp Phe Arg
                            90
. 85
Leu Met His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
                        105
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
                      120
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150
                    155
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                            170
                                     175
            165
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
                185 190
         180
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200
Thr Val Ala Pro Thr Glu Ala
 210
<210> 137
<211> 215
<212> PRT
<213> Homo sapiens
```

```
<400> 137
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                                10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                        40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
             55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
        70
                         75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Met Ile
              85
                               90
His Pro Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
                            105
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
                         120
                                           125
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
                     135
                          140
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
              150 155
Ala Gly Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
             165
                               170
                                                 175
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
         180 . 185
                                            190
Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
               200
Thr Val Ala Pro Thr Glu Ala
 210
<210> 138
<211> 213
<212> PRT
<213> Homo sapiens
<400> 138
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
                                10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
         20
                            25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                        40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                    55
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
      70
                                   75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Phe Pro Val
      . 85
                               90
Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
```

```
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
   115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
           135
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
              150
                         155
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                  170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
                            185
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
    195
                         200
Ala Pro Thr Glu Ala
  210
<210> 139
<211> 213
<212> PRT
<213> Homo sapiens
<400> 139
Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
              5
                                10
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
                            25
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
                        40
Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
                     55
                                       60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
                                   75
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Asp Asn Pro Tyr
                                90
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
         100
                           105
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
                       120
                                       125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
            135
                            140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
                150
                                  155
Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
            165
                               170
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
                  185
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
      195
Ala Pro Thr Glu Ala
   210
```

```
<210> 140
 <211> 217
 <212> PRT
 <213> Homo sapiens
 <400> 140 ·
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
                                    10
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20
                                25
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
                            40
 Ser Ala Ile Ser Gly Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
                        55
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
                    70
                                       75
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                                    90
Ala Arg Phe Met Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser
           100
                                105
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
       115
                            120
                                               125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
                        135
                                         140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
                   150
                                       155
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
               165
                                   170
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
           180
                               185
                                                   190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
                           200
Lys Lys Val Glu Pro Lys Ser Glu Phe
  210
<210> 141
<211> 217
<212> PRT
<213> Homo sapiens
<400> 141
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
                                   10
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
                               25
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
Ser Ala Ile Ser Gly Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
                       55
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
```

```
70
                                     75
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                                 90
Ala Arg Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
          100
                             105
                                                110
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
                                  125
                        120
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
                     135
                                       140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
               150
                                   155
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
                                170
             165
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
                          185
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
               200
Lys Lys Val Glu Pro Lys Ser Glu Phe
210
<210> 142
<211> 217
<212> PRT
<213> Homo sapiens
<400> 142
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
                                 10
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
                             25
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
Ser Ala Ile Ser Gly Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
                     55
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 · 70
                                75
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                                 90
Ala Arg Phe Leu Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser
          100
                             105
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
                         120
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
                      135
                                        140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150
                                    155
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
           165 ·
                                170
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
                             185 ·
```

```
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
                   200
Lys Lys Val Glu Pro Lys Ser Glu Phe
  210
                     215
<210> 143
<211> 221
<212> PRT
<213> Homo sapiens
<400> 143
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
                                10
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
                            25
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
                                            45
                         40
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
                   55
                                       60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
              70
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                                 90
Ala Arg Thr Phe Pro Ile Asp Ala Asp Ser Trp Gly Gln Gly Thr Leu
           100
                             105
                                                110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
                                            125
                          120
       115
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
                                       140
                     135
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
                 150
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
             165
                                170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
                  185 190
          180
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
           200
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
                     215
<210> 144
<211> 218
<212> PRT
<213> Homo sapiens
<400> 144
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
                               10
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
```

```
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
                      55
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                                 90
Ala Arg Gly His Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
                            105
Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
                         120
                                            125
 115
Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
                                 140
 130 135
Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
               .150
                                    155
145
Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
                                  170
Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
                              185
           180
Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
      195
                          200
Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
   210
                      215
<210> 145
<211> 222
```

<212> PRT

<213> Homo sapiens

<400> 145

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 10 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr 25 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val 55 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 70 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 90 85 Ala Arg Tyr Trp Arg Gly Leu Ser Phe Asp Ile Trp Gly Gln Gly Thr 105 100 Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro 120 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly 135 140 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn

```
145
                  150
                                     155
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
        165
                                170
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
           180
                             185
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
    195
               200
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
                      215
<210> 146
<211> 217
<212> PRT
<213> Homo sapiens
<400> 146
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1
               5
                                 10
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
                             25
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
                         40
                                            45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
                     55
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
              70
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
              85
                                 90
Ala Arg Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
                            105
           100
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
                         120
                                           125
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
                      135
                                        140
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
        150
                                    155
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
             165
                               170
                                                    175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
                            185 190
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
                        200
Lys Lys Val Glu Pro Lys Ser Glu Phe
  210
<210> 147
<211> 225
<212> PRT
<213> Homo sapiens
```

```
<400> 147
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
                            40
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
                       55
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
                                      75
                   70
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                                   90
Ala Arg Gly Leu Tyr Trp Ala Val Tyr Pro Tyr Phe Asp Phe Trp Gly
                              105
                                                   110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
                          120
                                              125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
                                          140
                       135
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                150
                                      155
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
              165
                                   170
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
                               185
                                                   190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
                            200
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
                                           220
                        215
Phe
225
<210> 148
<211> 224
<212> PRT
<213> Homo sapiens
<400> 148
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
                       55
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
                                      75
```

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

```
Ala Arg Leu Asp Thr Tyr Tyr Pro Asp Leu Phe Asp Tyr Trp Gly Gln
                          105
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
                         120
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                     135
                            140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                          155
       150
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                               170
             165
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
         180
                            185
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
                         200
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
                            . 220
                     215
<210> 149
<211> 220
<212> PRT
<213> Homo sapiens
<400> 149
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
           20
                             25
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
       35
                         40
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
                      55
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
                  70
                                     75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                                90
              85
Ala Arg Thr Tyr Tyr Phe Asp Ser Trp Gly Gln Gly Thr Leu Val
                             105
                                                110
          100
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
                         120
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
                      135
                                         140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
               150
                                    155
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                                170
             165
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
                          185
          180
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
                         200
```

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe

220 210 215 <210> 150 <211> 224 <212> PRT <213> Homo sapiens <400> 150 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 10 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr 20 25 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 40 45 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val 55 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 70 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 95 90 Ala Arg Tyr Met Ala Tyr Met Ala Glu Ala Ile Asp Val Trp Gly Gln 100 105 110 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val 120 125 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala 135 140 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser 150 155 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val 170 165 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro 185 180 190 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys 200 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe 210 215 220 <210> 151 <211> 230 <212> PRT <213> Homo sapiens <400> 151 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala 10 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr 25 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 40

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe

```
55
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
            85
                               90
Ala Arg Leu Val Gly Ile Val Gly Tyr Lys Pro Asp Glu Leu Leu Tyr
                           105
Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
              120
                                125
Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
          135
                                      140
Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
       . 150
                                  155
Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
             165
                      170
                                                  175
His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
                           185
Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
      195 200
                                          205
Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
  210 215
Glu Pro Lys Ser Glu Phe
225
<210> 152
<211> 222
<212> PRT
<213> Homo sapiens
<400> 152
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
                                10
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
                        40
Ser Ala Ile Ser Gly Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
                  55
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
                                  75
               70
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                               90
Ala Arg Tyr Gly Ala Tyr Phe Gly Leu Asp Tyr Trp Gly Gln Gly Thr
                           105
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
                        120
                                  125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 130 135
                             140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
                 150
```

```
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
             165
                              170
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
          180
                          185
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
 195
                       200
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215
<210> 153
<211> 225
<212> PRT
<213> Homo sapiens
<400> 153
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
 20
                          25
Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
                    40
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
                 55
                             60
Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
               70
                                  75
Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
            85
                              90
Tyr Tyr Cys Ala Arg Gly Tyr Ala Asp Ile Ser Phe Asp Tyr Trp Gly
         100 105
                                           110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
                      120
                                        125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
                    135
                                    140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                150
                                 155
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
   165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180
                          185
                                190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195
                       200
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
                 215
                                    220
Phe
225
<210> 154
<211> 220
<212> PRT
<213> Homo sapiens
```

```
<400> 154
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
         20
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
                 70
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
             85
Ala Arg Tyr Tyr Leu Leu Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val
        100 105
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
                                 125
 115
                       120
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
                               140
                    135
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
        Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
       165 170
                                                 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
         180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
                         200
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
                     215
<210> 155
<211> 229
<212> PRT
<213> Homo sapiens
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
                               10
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
                            25
          20
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
                         40
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
                     55
                                      60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
                                75
                 70
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
```

90

Ala Arg Trp Ser Asp Gln Ser Tyr His Tyr Tyr Trp His Pro Tyr Phe

85

```
105
          100
Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
                120
                                            125
    115
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
                    135
                                        140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                 150
                                  155
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                                170 , 175
             165
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
                            185
          180
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
                      200
 195
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
                     215
 210
                              .
Pro Lys Ser Glu Phe
225
<210> 156
<211> 220
<212> PRT
<213> Homo sapiens
<400> 156
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
                                 10
                                                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
                              25
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
                                            45
                         40
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
                      55
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
                                     75
               70
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                                 90
Ala Arg Leu Ile Gly Tyr Phe Asp Leu Trp Gly Gln Gly Thr Leu Val
                            105
                                                110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
                         120
                                             125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
                     135
                                         140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
               150
                                    155
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                                 170
               165
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Leu
          180 185
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
       195 . . 200
```

```
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
  210 215 . 220
<210> 157
<211> 225
<212> PRT
<213> Homo sapiens
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
                                10
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
                             25
         20
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
                         40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                     55
                                      60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
                          · 75
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                        90
             85
Ala Arg Leu Thr Asn Tyr Phe Asp Ser Ile Tyr Tyr Asp His Trp Gly
          100 105
                                               110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
                        120
                                           125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
                     135
                                        140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                                    155 160
                  150
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
              165
                                170
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
                             185
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
                                           205
                         200
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
                     215
Phe
225
<210> 158
<211> 225
<212> PRT
<213> Homo sapiens
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
                                10
              5
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
         20
```

```
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
                         40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                     55
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                         90
Ala Arg Leu Val Gly Gly Gly Tyr Asp Leu Met Phe Asp Ser Trp Gly
                         105
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
     115 120 125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135
                                      140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150
                                    155
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                                170
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
                            185
          180
Pro Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
. 195
                         200
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
                    215
Phe
225
<210> 159
<211> 226
<212> PRT
<213> Homo sapiens
<400> 159
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
                                10
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
                             25
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
                         40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                                       60
                     55
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
               70
                                    75
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                             90
Ala Arg Tyr Val Thr Tyr Gly Tyr Asp Asp Tyr His Phe Asp Tyr Trp
                            105
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
              120
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
```

```
140
                      135
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                                   155
                 150
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                              170
           165
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
                          185
    180
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
                       200
                                           205
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
                     215
Glu Phe
225
<210> 160
<211> 219
<212> PRT
<213> Homo sapiens
<400> 160
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5
                                 10
                                          15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
                             25
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
                  55
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
                                    75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                                90
              85
Ala Arg Ser Gly Tyr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
                            105
         100
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
                         120
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
                      135
                                         140
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
                                  155
        150
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
              165
                                170
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
                          185
          180
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
                        200
Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
```

<210> 161

```
<211> 231
<212> PRT
<213> Homo sapiens
<400> 161
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
                                  10
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
                             25
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
                          40
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
                      55
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
               70
                                  75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                                90
Ala Arg Tyr Ile Gly Tyr Thr Asn Val Met Asp Ile Arg Pro Gly Phe
           100
                          . 105
                                                110
Tyr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
                          120
                                             125
Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
                     135
                                         140
Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
               150
                                     155
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
              165
                                 170
                                                    175
Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
                             185
                                                190
Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
   195
                         200
Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
  210 215
                            220
Val Glu Pro Lys Ser Glu Phe
<210> 162
<211> 225
<212> PRT
<213> Homo sapiens
<400> 162
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
                                 10
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
                             25
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
                         40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
```

55

```
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
                 70
                                     75
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
Ala Arg Phe Arg Ala Tyr Gly Asp Asp Phe Tyr Phe Asp Val Trp Gly
                             105
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
                         120
                                            125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
                     135
                                       140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150
                                 155
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
          165
                   170
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
         180
                            185
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
                         200
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
         215
225
<210> 163
<211> 228
<212> PRT
<213> Homo sapiens
<400> 163
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 .
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
                     55
                                        60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
                 70
                                    75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
     . 85 .
                                 90
Ala Arg Ile Met Trp Ser Asp Tyr Gly Gln Leu Val Lys Gly Gly Asp
                             105
Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
                         120
                                            125
Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
  130
           135
                                       140
Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
               150
                                    155
```

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr

```
165
                               170
Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
                  185
  180
                                         190
Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
 195 200
Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
                   215
Lys Ser Glu Phe
<210> 164
<211> 224
<212> PRT
<213> Homo sapiens
<400> 164
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
                               10
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                    55
                                     60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
                     75
65 70
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                              90
Ala Arg Tyr Tyr Val Thr Asp Thr Ala Tyr Phe Asp Tyr Trp Gly Gln
       100
               105
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
   115 120
                                        125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                   135
                                    140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                150
                                  155
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
             165
                               170
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180
                          185
                                          190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
                     200
                            205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
<210> 165
<211> 224
<212> PRT
<213> Homo sapiens
```

```
<400> 165
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
                                  10
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
                             25
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
                                              4.5
                          40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                      55
                                          60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
                   70
                                      75
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                                  90
Ala Arg His Asp Phe Asp Gly Ser Ile Phe Met Asp Phe Trp Gly Gln
                              105
                                                 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
                          120 .
                                             125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                       135
                                         140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                                     155
                  150
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
              165
                                 170
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
                              185
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
                         200
                                    205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
<210> 166
<211> 225
<212> PRT
<213> Homo sapiens
<400> 166
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
                                  10
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
                           40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                       55
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
                               . 75
                   70
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                                  90
Ala Arg Tyr Ala Gly His Gln Tyr Glu Phe Phe Asp Phe Trp Gly
                              105 .
```

```
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
     115
           120
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
                     135
                                        140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                 150
                                    155
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
    165
                   170
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
                185
         180
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
                        200
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
                     215
225
<210> 167
<211> 224
<212> PRT
<213> Homo sapiens
<400> 167
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
                                 10
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
                             25
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
                         40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                                60
  50 55
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 . 70
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                                90
Ala Arg Leu Tyr Ala Asp Ala Asp Ile Tyr Phe Asp Tyr Trp Gly Gln
                           105
          100
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
                        120
                                           125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                     135
                                        140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                 150
                                    155
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
              165
                                170
Leu Glm Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
                          185
          180
                                               190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
                        200
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
```

215 220 210 <210> 168 <211> 222 <212> PRT <213> Homo sapiens <400> 168 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser 10 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr 20 25 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 40 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe 55 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys 90 Ala Arg Thr Lys Tyr Val Gly Ser Glu Asp Val Trp Gly Gln Gly Thr 105 110 100 Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro 115 120 125 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly 135 140 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn 150 155 Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln 170 165 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser 180 185 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser 200 Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe <210> 169 <211> 222 <212> PRT <213> Homo sapiens <400> 169 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu 10 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr 20 25 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met 40

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

```
55
                                       60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
                                  75
        70
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
            85
                               90
Ala Arg Tyr Arg Tyr Pro His Met Phe Asp Phe Trp Gly Gln Gly Thr
         100
                         105
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
                        120
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
                     135
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
                 150
                                 155
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                         170
          165
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
                  185
          180
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
                      200
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
<210> 170
<211> 224
<212> PRT
<213> Homo sapiens
<400> 170
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
                             25
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
          40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                     55
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
                                    75
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
             85
                               90
Ala Arg Leu Phe Ala Gly Leu Glu Leu Tyr Phe Asp Tyr Trp Gly Gln
                           105
                                             110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
   115 120
                                          125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                     135
                                       140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150
                            155
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                               170 . 175
              165
```

```
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
          180
                         185
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
                        200
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210 215
·<210> 171
<211> 221
<212> PRT
<213> Homo sapiens
<400> 171
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
                                 10
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
          20
                            25
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
                         40
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
                    - 55
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
                 70
                                 75
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
          85 90
Ala Arg Gly Gly Phe Phe Asn Met Asp Tyr Trp Gly Gln Gly Thr Leu
          100
                 105
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
                         120
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
                      135
                                        140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
                  150
                                   155
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                                170
             165
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
                            185
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
                        200
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
  210 . 215
<210> 172
<211> 223
<212> PRT
<213> Homo sapiens
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
                                10
```

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
                  25
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
                 55
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
          70 75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
          8.5
                 90
Ala Arg Gly Tyr Ile Pro Tyr His Leu Phe Asp Tyr Trp Gly Gln Gly
                 . 105
          100
                                             110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
                         120
                                          125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
                     135
                                     140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150
                        155
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
             165
                               170
                                                 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
         180
                           185
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
                      200
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
<210> 173
<211> 225
<212> PRT
<213> Homo sapiens
<400> 173
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
```

20 25 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met 40 Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe 55 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys 85 90 Ala Arg Tyr Tyr Gly Phe Glu Tyr Asp Leu Leu Phe Asp Asn Trp Gly 100 105 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser 120 125 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala

```
. 140
                    135
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
        150
                             155
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
             165
                             170
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
                           185
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
              200
                                 . 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
           215
                              220
Phe
225
<210> 174
<211> 221
<212> PRT
<213> Homo sapiens
<400> 174
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5
                                10
                                         15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
                           25
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
                       40
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
                    55
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
                70
                                   75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                               90
             85
Ala Arg Ile Thr Tyr Ile Gly Tyr Asp Phe Trp Gly Gln Gly Thr Leu
         100
                           105
                                             110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
                        120
                                          125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
                     135
                                       140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
                150
                                  155
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
          165
                              170
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
       180
                 185
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
    195 200
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
  210
                    215
```

<210> 175

```
<211> 220
<212> PRT
<213> Homo sapiens
<400> 175
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
                                 10
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
         20
                            25
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
                         40
                                            45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
                      55
                                         60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
              85
                                 90
Ala Arg Gln Glu Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
           100
                             105
                                                110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
                         120
       115
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
                     135 ·
                                        140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
                 150
                                  155
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
              165 .
                                170
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
          180 185
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 195 200 205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
<210> 176
<211> 224
<212> PRT
<213> Homo sapiens
<400> 176
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
                                 10
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
                         40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                     55
                                       60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
```

```
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                                90
Ala Arg Leu Tyr Pro Glu Asp Leu Ile Tyr Phe Asp Tyr Trp Gly Gln
       100
                 105
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
                        120
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                    135
                         140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                150
                                   155
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                   170
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
  180
                  185
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
                     215
<210> 177
<211> 231
<212> PRT
<213> Homo sapiens
<400> 177
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1
                                10
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
         20
                            25
Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
                    55
Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
              70 ·
                                   75
Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
             85
                               90
Tyr Tyr Cys Ala Arg Trp Met Thr Pro Pro Gly His Tyr Tyr Gly Tyr
          100
                            105
                                              110
Thr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
```

120

135

150

165

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu 180 185 190 Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr

125

140

155

170

```
200
       195
Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
 210 215
                                     220
Val Glu Pro Lys Ser Glu Phe
<210> 178
<211> 225
<212> PRT
<213> Homo sapiens
<400> 178
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5
                     10
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
                             25
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
       35
                                           45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                     55
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
                  70
                                    75
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
           85
                  90
                                                  95
Ala Arg Leu Arg Val His Asp Tyr Ala Met Tyr Phe Asp Leu Trp Gly
                           105
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
                        120
                                           125
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
                     135
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 - 150
                                   155
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                      170
             165
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        180
                            185
                                     190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195
                         200
                                           205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
                    215
                                        220
Phe
225
<210> 179
<211> 226
<212> PRT
<213> Homo sapiens
<400> 179
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
```

```
10
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
                               25
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
                           40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                       55
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                                  90
Ala Arg Phe Val Ser Tyr Asn Gly Ser Val Pro Tyr Phe Asp Tyr Trp
                              105
          100
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
                          120
                                              125
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
                      135
                                          140
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                  150
                                       155
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                                   170
               165
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
                               185
Val Pro Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
                           200
                                               205
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
                       215
Glu Phe
225
<210> 180
<211> 224
<212> PRT
<213> Homo sapiens
<400> 180
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
                           40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                       55
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
                                      75
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                                  90
Ala Arg Ile Ile Gly Asp Tyr Val Ile Phe Phe Asp Val Trp Gly Gln
```

```
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
                         120
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                     135
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
     150
                             155
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
             165
                                170
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
          180
                            185
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
                         200
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
                     215
<210> 181
<211> 224
<212> PRT
<213> Homo sapiens
<400> 181
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
          20
                             25
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35
                         40
                                            45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
                     55
                           60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
              85
                                90
Ala Arg Leu Phe Thr Tyr Pro Phe Leu Tyr Phe Asp Val Trp Gly Gln
         100 105
                                               110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
                         120
                                            125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                     135
                                        140 -
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                 150
                                     155
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
             165
                                170
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
         180
                            185
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
                        200
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
```

```
<210> 182
<211> 224
<212> PRT
<213> Homo sapiens
<400> 182
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
                 · 10
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
             40
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
. 50 55
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
             70
                       75
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                          90
Ala Arg Ile Leu Thr Gly His Val Leu Leu Phe Asp Tyr Trp Gly Gln
                         105
                                110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
   115
                      120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
             165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
                185
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu Phe
 210
                  215
<210> 183
<211> 27
<212> DNA
<213> Homo sapiens
<400> 183
cagagetatg actateagea gtttact
                                                         27
<210> 184
<211> 26
<212> DNA
<213> Homo sapiens
<400> 184
```

26

cagagetatg actttaagae ttatet

<210> 185 <211> 26 <212> DNA <213> Homo	sapiens		
<400> 185 cagagetatg	actttcttcg	ttttc	26
<210> 186 <211> 27 <212> DNA <213> Homo	sapiens		
<400> 186 cagagetatg	actttattaa	tgttatt	27
<210> 187 <211> 27 <212> DNA			
<213> Homo	sapiens		
<400> 187 cagagctatg	actttgttcg	ttttatg	27
<210> 188 <211> 27 <212> DNA <213> Homo	eanione		
<400> 188	saprens		
	acttttataa	gtttaat	27
<210> 189 <211> 27 <212> DNA			
<213> Homo	sapiens		
<400> 189 cagagetatg	actttcgtcg	ttttct	27
<210> 190 <211> 27 <212> DNA <213> Homo	sapiens		
<400> 190	actttaatcg	tggtcct	27
(010) 101	•		

<211> <212> <213>	DNA	sapiens		
<400> cagago		accagcgtaa	gtgg	24
<210> <211> <212> <213>	24 DNA	sapiens		
<400> cagcag		atggtacttc	tgtt	24
<210> <211> <212>	27 DNA			
<213>	Homo	sapiens		
<400> cagago		acggttttaa	gactcat	27
<210><211><211><212>	24 DNA		•	
<213>	Homo	sapiens		
<400> cagago		actattctct	tctt	24
<210> <211> <212>	24			
<213>	Homo	sapiens		
<400> cagago		actttaattt	tcat	24
<210> <211> <212>	30 DNA			
<213>	ното	sapiens		
<400> cagago		acatgattgc	tcgttatcct	30
<210> <211> <212>	30			

<213> Homo	sapiens		
<400> 197 cagagctggg	acattcatcc	ttttgatgtt	30
<210> 198 <211> 24 <212> DNA <213> Homo	sapiens		
<400> 198 cagagetggg	accttgagcc	ttat	24
<210> 199 <211> 27 <212> DNA <213> Homo	sapiens		
<400> 199 cagagctatg	acgttcttga	ttctgag	27
<210> 200 <211> 30 <212> DNA <213> Homo	sapiens		
<400> 200 cagagctatg	acccttctca	tccttctaag	30
<210> 201 <211> 24 <212> DNA <213> Homo	sapiens		
<400> 201 cagagctatg	acgatatgca	gttt	24
<210> 202 <211> 27 <212> DNA <213> Homo	sapiens		
<400> 202 cagagetggg	acattaatca	tgctatt	27
<210> 203 <211> 27 <212> DNA <213> Homo	sapiens		

WO 02/	086085	PCT/US02/	12801
<400> 203 cagagctatg	actattatga	ttatggt	27
<210> 204 <211> 24 <212> DNA <213> Homo	sapiens		
<400> 204	atgattttcc	tatt	24
<210> 205 <211> 30 <212> DNA	_		
<213> Homo	sapiens		
<400> 205 cagagetggg	acaatcttaa	gatgcctgtt	30
<210> 206 <211> 30 <212> DNA <213> Homo	sapiens		
<400> 206 cagagctatg	acgtttttcc	tattaatcgt	30
<210> 207 <211> 21 <212> DNA			
<213> Homo	sapiens		
<400> 207 cagagcgatc	tttattttcc	t	21
<210> 208 <211> 24 <212> DNA <213> Homo	sapiens		
<400> 208 cagagctatg	acgttactcc	tcgt	24
<210> 209 <211> 27 <212> DNA <213> Homo	saniens		
<400> 209	Capacita	·	
	accctgttgg	ttttcct	27

<210> 210 <211> 24 <212> DNA <213> Homo	sapiens		٠
<400> 210 cagagetatg	acctttctcc	tcgt	24
<210> 211 <211> 30 <212> DNA <213> Homo	sapiens		
<400> 211 cagagctatg	acttttctca	ttatttttt	30
<210> 212 <211> 27 <212> DNA <213> Homo	eaniene		
<400> 212	accttcgtta	ttctcat	27
<210> 213 <211> 24 <212> DNA <213> Homo	٠,		
<400> 213 cagagetatg	accttcgtaa	tcgt	24
<210> 214 <211> 27 <212> DNA <213> Homo	sapiens		-
<400> 214 cagagetatg	actttactta	tggttct 2	27
<210> 215 <211> 24 <212> DNA <213> Homo	sapiens		
<400> 215 cagcagttta	atgattctcc	ttat 2	24
<210> 216			

		•	
<211> 27			
<212> DNA			
<213> Homo	sapiens		
	•		
<400> 216	•	,	
cagagetatg	acatttctgg	ttatcct	27
2 2 2	33		
<210> 217			
<211> 30			
<212> DNA			
<213> Homo	sapiens		
<400> 217			
cagagccgtg	acctttatta	tgtttattat	30
<210> 218			
<211> 24			
<212> DNA	•		
<213> Homo	sapiens		
<400× 210			
<400> 218	2000++0+2+	ataa	24
cagagerary	accgttctat	gegg	24
<210> 219		1	
<211> 27			
<212> DNA			
<213> Homo	sapiens		
	- -		
<400> 219			
cagagetggg	acgttcagac	tgataag	27
<210> 220			
<211> 27			
<212> DNA			
<213> Homo	sapiens		
<400> 220			0.7
cagagetggg	acccttctca	ttattat	27
<210> 221			
<211> 27			
<212> DNA			
<213> Homo	saniens		
.LLO: MOMO			
<400> 221			
	acattatgcc	tgagcgt	27
	J		
<210> 222		•	
<211> 27	•		
<212> DNA			

					•	
<213> Homo	sapiens					
<400> 222 cagagcatgg	actttcgtct	tatgcat				27
<210> 223 <211> 27		•.				
<212> DNA <213> Homo	sapiens					
<400> 223 cagagetttg	acatgattca	tccttat				27
<210> 224 <211> 21 <212> DNA						
<213> Homo	sapiens					
<400> 224 cagagcgact	ttcctgttat	g				21
<210> 225 <211> 21 <212> DNA						
<213> Homo	sapiens				•	
<400> 225 cagagcgaca	atccttatct	t				21
<210> 226 <211> 12 <212> DNA				·		
<213> Homo	sapiens					
<400> 226 tttatggata	tt					12
<210> 227 <211> 12 <212> DNA						
<213> Homo	sapiens					
<400> 227 ggttttgatt	at	•				12
<210> 228 <211> 12 <212> DNA						
<213> Homo	sapiens					

<400> 228 tttcttgata	tt				12
<210> 229 <211> 24 <212> DNA <213> Homo	sapiens				
<400> 229 acttttccta	ttgatgctga	ttct			24
<210> 230 <211> 15 <212> DNA <213> Homo	sapiens				
<400> 230 ggtcatgttg	attat				15
<210> 231 <211> 27 <212> DNA <213> Homo	sapiens				
<400> 231 tattggcgtg	gtctttcttt	tgatatt			27
<210> 232 <211> 12 <212> DNA <213> Homo	sapiens				
<400> 232 ttttttgatt	at ,				12
<210> 233 <211> 36 <212> DNA <213> Homo	sapiens				
<400> 233 ggtctttatt	gggctgttta	tccttatttt	gatttt		36
<210> 234 <211> 33 <212> DNA <213> Homo	sapiens				
<400> 234 cttgatactt	attatcctga	tctttttgat	tat		33

<210> 235 <211> 21 <212> DNA <213> Homo	sapiens					
<400> 235						
	attttgattc	t				21
<210> 236 <211> 33 <212> DNA <213> Homo	saniens					
<400> 236	,					
	atatggctga	ggctattgat	gtt	•		33,
<210> 237 <211> 51 <212> DNA						
<213> Homo	sapiens					
<400> 237 cttgttggta	ttgttggtta	taagcctgat	gagcttcttt	attttgatgt	t	51
<210> 238 <211> 27 <212> DNA <213> Homo	sapiens					
<400> 238 tatggtgctt	attttggtct	tgattat				27
<210> 239 <211> 27 <212> DNA <213> Homo	sapiens			·		
<400> 239 ggttatgctg	atatttcttt	tgattat				27
<210> 240 <211> 21 <212> DNA <213> Homo	sapiens				·	
<400> 240 tattatcttc	ttcttgatta	t				21
<210> 241						

<211> 48 <212> DNA <213> Homo	sapiens				
<400> 241 tggtctgatc	agtcttatca 1	ttattattgg	catccttatt	ttgatgtt	48
<210> 242 <211> 21 <212> DNA <213> Homo	sapiens			•	
<400> 242 cttattggtt	attttgatct t	t			21
<210> 243 <211> 36 <212> DNA <213> Homo	sapiens				
<400> 243	attttgattc t	tatttattat	gatcat		36
<210> 244 <211> 36 <212> DNA <213> Homo					
<400> 244	gtggttatga t	tettatettt	gattet		36
<210> 245 <211> 39 <212> DNA <213> Homo			344404		
<400> 245	·				

tatgttactt atggttatga tgattatcat tttgattat

<210> 246 <211> 18 <212> DNA

<400> 246

<210> 247 <211> 54 <212> DNA

<213> Homo sapiens

tctggttatc ttgattat

PCT/US02/12801

39

18

<213>	Homo	sapiens					
<400> tatatt		atactaatgt	tatggatatt	cgtcctggtt	tttatcttga	ttat	54
<210><211><211><212><213>	36 DNA	sapiens		·			
		oapremo	·				
<400> tttcgt		atggtgatga	ttttattt	gatgtt		•	36
<210><211><211><212><213>	45 DNA	sapiens					
		saprens					
<400> attato		ctgattatgg	tcagcttgtt	aagggtggtg	atatt		45
<210><211><211><212><213>	33 DNA	sapiens					
<400> tattat		ctgatactgc	ttattttgat	tat			33
<210> <211> <212>	33				٠		
<213>	Ното	sapiens				•	
<400> catgat		atggttctat	ttttatggat	ttt	•		33
<210> <211> <212> <213>	36 DNA	sapiens		·			
<400>					٠		26
tatget	ggtc	atcagtatga	gtttttttt	gatttt			36
<210> <211> <212>	33 DNA						
<513>	ното	sapiens					

<400> 253 ctttatgctg	atgctgatat	ttattttgat	tat		33
<210> 254 <211> 27 <212> DNA <213> Homo	sapiens				
<400> 254 actaagtatg	ttggttctga	ggatgtt			27
<210> 255 <211> 27 <212> DNA <213> Homo	sapiens				
<400> 255 tatcgttatc	ctcatatgtt	tgatttt			27
<210> 256 <211> 33 <212> DNA <213> Homo	sapiens				
<400> 256 ctttttgctg	gtcttgagct	ttattttgat	tat		33
<210> 257 <211> 24 <212> DNA <213> Homo	sapiens				
<400> 257 ggtggttttt	ttaatatgga	ttat			24
<210> 258 <211> 30 <212> DNA <213> Homo	sapiens			7	
<400> 258 ggttatattc	cttatcatct	ttttgattat			30
<210> 259 <211> 36 <212> DNA					
<213> Homo <400> 259	sapiens				
tattatggtt	ttgagtatga	tcttctttt	gataat		36

<210> 260 <211> 24 <212> DNA		
<213> Homo sapiens		
<400> 260 attacttata ttggttatga	tttt	24
<210> 261 <211> 21 <212> DNA		
<213> Homo sapiens		
<400> 261 caggagtggt atatggatta	. t	21
<210> 262 <211> 33 <212> DNA		
<213> Homo sapiens		
<400> 262 ctttatcctg aggatcttat	ttattttgat tat	33
<210> 263 <211> 45 <212> DNA <213> Homo sapiens		
<400> 263 tggatgactc ctcctggtca	ttattatggt tatacttttg atgtt	45
<210> 264 <211> 36 <212> DNA <213> Homo sapiens		
<400> 264 cttcgtgttc atgattatgc	tatgtatttt gatctt	36
<210> 265 <211> 39 <212> DNA <213> Homo sapiens		
<400> 265 tttgtttctt ataatggttc	tgttccttat tttgattat	39
<210> 266		

<211> 33 <212> DNA <213> Homo	sapiens					
<400> 266 attattggtg	attatgttat	: tttttttgat	: gtt			33
<210> 267 <211> 33 <212> DNA						
<213> Homo	sapiens					
<400> 267 ctttttactt	atccttttct	ttattttgat	gtt			33
<210> 268 <211> 33 <212> DNA						
<213> Homo	sapiens					
<400> 268 attcttactg	gtcacgttct	tctttttgat	tat			33
<210> 269 <211> 645 <212> DNA <213> Homo	sanjene					
<400> 269	Saprens					
caggtgcaat agctgcgcgg cctgggaagg gcggatagcg	cctccggatt gtctcgagtg tgaaaggccg acagcctgcg gccaaggcac tggctccgag attatttcc atacctttcc tgccgagcag	cagcaaaagc ggaaccagtc ggcggtgctg cagcttaggc	agctatgcga attagcggta tcacgtgata acggccgtgt gttagctcag accagcggcg accgtgagct caaagcagcg actcagacct	tgagctgggt gcggcggcag attcgaaaaa attattgcgc cgtcgaccaa gcacggctgc ggaacagcgg gcctgtatag atatttgcaa	gcgccaagcc cacctattat caccctgtat gcgttttatg aggtccaagc cctgggctgc ggcgctgacc cctgagcagc	60 120 180 240 300 360 420 480 540 600 645
<210> 270 <211> 645 <212> DNA <213> Homo s	sapiens					
<400> 270						
caggtgcaat t agctgcgcgg c cctgggaagg c	cctccggatt	tacctttagc	agctatgcga	tgagctgggt	gcgccaagcc	60 120 180

geggatageg to ctgcaaatga gattattggg gtgtttccgc to ctggttaaag aageggegtge agtgtgaceg taaaccgagea a	acagcetgeg gccaaggeae tggeteegag attattteee atacetttee tgeegageag	tgcggaagat cctggtgacg cagcaaaagc ggaaccagtc ggcggtgctg cagcttaggc	acggccgtgt gttagctcag accagcggcg accgtgagct caaagcagcg actcagacct	attattgcgc cgtcgaccaa gcacggctgc ggaacagcgg gcctgtatag atatttgcaa	gcgtggtttt aggtccaagc cctgggctgc ggcgctgacc cctgagcagc	3 3 4 4 5 6	40 00 60 20 80 40 600
<210> 271 <211> 645 <212> DNA <213> Homo s	sapiens						
<400> 271 caggtgcaat tagctgcgcgg cctgggaagg gcggatagcg tctgcaaatga gatatttggg gtgtttccgc tctggttaaag agcggcgtgc aaaaccgagca aaaaccgagca a	cctccggatt gtctcgagtg tgaaaggccg acagcctgcg gccaaggcac tggctccgag attatttccc atacctttcc	tacctttagc ggtgagcgcg ttttaccatt tgcggaagat cctggtgacg cagcaaaagc ggaaccagtc ggcggtgctg cagcttaggc	agctatgcga attagcggta tcacgtgata acggccgtgt gttagctcag accagcggcg accgtgagct caaagcagcg actcagacct	tgagctgggt gcggcggcag attcgaaaaa attattgcgc cgtcgaccaa gcacggctgc ggaacagcgg gcctgtatag atatttgcaa	gcgccaagce cacctattat caccctgtat gcgttttctt aggtccaagc cctgggctgc ggcgctgacc cctgagcagc	1 2 3 3 4 4 5 6	60 20 80 40 60 20 80 40 00
<210> 272 <211> 657 <212> DNA <213> Homo s	sapiens						
<400> 272 caggtgcaat tagctgcgcggcgcaagggcgatagggcgcaaatgaggcgctgagggggggcgctgaaggggggcgctgaaacgtgaaccaagacctgagcaaacgtgaaccaa	cctccggatt gtctcgagtg tgaaaggccg acagcctgcg ctgattcttg gcgtgtttcc gcctggttaa ccagcggcgt gcgttgtgac	tacctttagc ggtgagcgcg ttttaccatt tgcggaagat gggccaaggc gctggctccg agattatttc gcataccttt cgtgccgagc	agctatgcga attagcggta tcacgtgata acggccgtgt accctggtga agcagcaaaa ccggaaccag ccggcggtgc agcagcttag	tgagctgggt gcggcggcag attcgaaaaa attattgcgc cggttagctc gcaccagcgg tcaccgtgag tgcaaagcag gcactcagac	gcgccaagcc cacctattat caccctgtat gcgtactttt agcgtcgacc cggcacggct ctggaacagc cggcctgtat ctatatttgc	1 2 3 3 4 4 5 6	60 20 80 40 60 20 80 40 57
<210> 273 <211> 648 <212> DNA <213> Homo s	sapiens						

<400> 272					
<400> 273 caggtgcaat tggtgg	2220 0000000000	ctaataceec	caaacaacsa	cctacatcta	60
agetgegegg ceteeg					120
					180
cctgggaagg gtctcg					240
gcggatagcg tgaaag					300
ctgcaaatga acagcc					360
gttgattatt ggggcc					420
agcgtgtttc cgctgg					420
tgcctggtta aagatt					
accagcggcg tgcata					540
agcgttgtga ccgtgc		the state of the s		caacgtgaac	600
cataaaccga gcaaca	ccaa agtggataaa	aaagtggaac	cgaaaagc		648
10105 024					
<210> 274					
<211> 660					_
<212> DNA			•		•
<213> Homo sapien	S				
<400> 274					
caggtgcaat tggtgg					60
agctgcgcgg cctccg					120
cctgggaagg gtctcg					180
gcggatagcg tgaaag					240
ctgcaaatga acagcc					300
cgtggtcttt cttttg	atat ttggggccaa	ggcaccctgg	tgacggttag	ctcagcgtcg	- 360
accaaaggtc caagcg					420
gctgccctgg gctgcc					480
agcggggcgc tgacca					540
tatagcctga gcagcg					600
tgcaacgtga accata	aacc gagcaacacc	aaagtggata	aaaaagtgga	accgaaaagc	660
<210> 275					
<211> 645					
<212> DNA					
<213> Homo sapien	s				
<400> 275					
caggtgcaat tggtgg					60
agetgegegg ceteeg					120
cctgggaagg gtctcg					180
gcggatagcg tgaaag					240
ctgcaaatga acagcc					300
gattattggg gccaag					360
gtgtttccgc tggctc					420
ctggttaaag attatt					480
agcggcgtgc atacct					540
gttgtgaccg tgccga				cgtgaaccat	600
aaaccgagca acacca	aagt ggataaaaaa	gtggaaccga	aaagc		645

<210> 276

```
<211> 669
<212> DNA
<213> Homo sapiens
<400> 276
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg
                                                                        60
agctgcaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc
                                                                       120
cctgggcagg gtctcgagtg gatgggcggc attattccga tttttggcac ggcgaactac
                                                                       180
gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat
                                                                       240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtggtctt
                                                                       300
tattgggctg tttatcctta ttttgatttt tggggccaag gcaccctggt gacggttagc
                                                                       360
tcagogtoga ccaaaggtoo aagogtgttt cogotggoto ogagoagoaa aagoaccago
                                                                       420
                                                                       480
gqcggcacgg ctgccctggg ctgcctggtt aaagattatt tcccggaacc agtcaccgtg
agctggaaca gcggggcgct gaccagcggc gtgcatacct ttccggcggt gctgcaaagc
                                                                       540
                                                                       600
ageggeetgt atageetgag eagegttgtg acegtgeega geageagett aggeaeteag
acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa
                                                                       660
                                                                       669
ccgaaaagc
<210> 277
<211> 666
<212> DNA
<213> Homo sapiens
<400> 277
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg
                                                                        60
agctgcgcgg cctccggatt tacctttagc agctatgcga tgagctgggt gcgccaagcc
                                                                       120
                                                                       180
cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat
                                                                       240
                                                                       300
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtcttgat
acttattatc ctgatctttt tgattattgg ggccaaggca ccctggtgac ggttagctca
                                                                       360
gegtegaeca aaggteeaag egtgttteeg etggeteega geageaaaag caccagegge
                                                                       420
                                                                       480
ggcacggctg ccctgggctg cctggttaaa gattatttcc cggaaccagt caccgtgagc
                                                                       540
tggaacagcg gggcgctgac cagcggcgtg catacctttc cggcggtgct gcaaagcagc
ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc
                                                                       600
                                                                       660
tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaccg
                                                                       666
aaaagc
<210> 278
<211> 654
<212> DNA
<213> Homo sapiens
<400> 278
                                                                        60
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg
agctgcaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc
                                                                       120
                                                                       180
cctgggcagg gtctcgagtg gatgggcggc attattccga tttttggcac ggcgaactac
gegeagaagt tteagggeeg ggtgaceatt acegeggatg aaageaceag cacegegtat
                                                                       240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtacttat
                                                                       300
tattattttg attettgggg ccaaggcace etggtgacgg ttageteage gtegaceaaa
                                                                       360
ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc
                                                                       420
```

ctgggctgcc tggtta gcgctgacca gcggcg ctgagcagcg ttgtga gtgaaccata aaccga	tgca tacctttccg ccgt gccgagcagc	gcggtgctgc agcttaggca	aaagcagcgg ctcagaccta	cctgtatagc tatttgcaac	480 540 600 654
<210> 279 <211> 666 <212> DNA <213> Homo sapier	ıs		·		
<400> 279 caggtgcaat tggtgg agctgcgcgg cctcgg gcggatagcg tgaaag gcttatatgg ctgag gcgtcgacca aaggtg ggcacggctg ccctgg tggaacagcg gggcgg ggcctgtata gcctga tatattgca acgtga aaaagc	gatt tacctttage gagtg ggtgagegeg ggtgageat tgeggaagat tgatgtttgg ecaag egtgtteeg ectgataaa etgae egttgtgaee	agctatgcga attagcggta tcacgtgata acggccgtgt ggccaaggca ctggctccga gattatttcc catacctttc gtgccgagca	tgagctgggt gcggcggcag attcgaaaaa attattgcgc ccctggtgac gcagcaaaag cggaaccagt cggcggtgct gcagcttagg	gcgccaagcc cacctattat caccctgtat gcgttatatg ggttagctca caccagcggc caccgtgagc gcaaagcagc cactcagacc	60 120 180 240 300 360 420 480 540 600 660
<210> 280 <211> 684 <212> DNA <213> Homo sapier	ı. Dis				
<400> 280 caggtgcaat tggttc agctgcaaag cctccg gcgcagaagt ttcagg ggtattgtg gttata agcaaaagca ccagcg agcaaaagca ccagcg gcggtgctgc agcttaggca ctcaga gataaaaaag tggaac	ggata tacctttacc gagtg gatgggctgg ggccg ggtgaccatg ttgcg tagcgaagat agcc tgatgagctt cagc gtcgaccaaa ggcgg cacggctgcc agctg gaacagcggg agcgg cctgtatagc accta tatttgcaac	agctattata attaacccga acccgtgata acggccgtgt ctttattttg ggtccaagcg ctgggctgcc gcgctgacca ctgagcagcg	tgcactgggt atagcggcgg ccagcattag attattgcgc atgtttgggg tgtttccgct tggttaaaga gcggcgtgca ttgtgaccgt	ccgccaagcc cacgaactac caccgcgtat gcgtcttgtt ccaaggcacc ggctccgagc ttatttcccg tacctttccg gccgagcagc	60 120 180 240 300 360 420 480 540 660 660 684
<210> 281 <211> 660 <212> DNA <213> Homo sapier	us			·	
<400> 281 caggtgcaat tggtgg	Jaaag cggcggcggc	ctggtgcaac	cgggcggcag	cctgcgtctg	60

agctgcgcgg	cctccggatt	tacctttagc	agctatgcga	tgagctgggt	gcgccaagcc	1	20
	gtctcgagtg						80
	tgaaaggccg					_	40 00
	acagcctgcg gtcttgatta						60
	caagcgtgtt						20
	gctgcctggt						80
agcggggcgc	tgaccagcgg	cgtgcatacc	tttccggcgg	tgctgcaaag	cageggeetg.	5	40
	gcagcgttgt						00
tgcaacgtga	accataaacc	gagcaacacc	aaagtggata	aaaaagtgga	accgaaaagc	6	60
<210> 282			•				
<211> 669							
<212> DNA							
<213> Homo	sapiens						
<400> 282							
	tgcaacagtc	taatccaaac	ctggtgaaac	cgagccaaac	cctgagcctg		60
	tttccggaga					1	20
	ggcgtggcct						80
	cggtgagcgt						40
	tgcaactgaa						00 60
	ctgatatttc ccaaaggtcc						20
	ctgccctggg						80
	geggggeget						40
	atagcctgag						00
	gcaacgtgaa	ccataaaccg	agcaacacca	aagtggataa	aaaagtggaa		60
ccgaaaagc						6	69
<210> 283							
<211> 654							
<212> DNA							
<213> Homo	sapiens						
<400> 283					•		
	tggtggaaag	cggcggcggc	ctggtgcaac	cgggcggcag	cctgcgtctg		60
	cctccggatt						20
	gtctcgagtg						80
	tgaaaggccg						40 00
	acagcctgcg attattgggg						60
	tgtttccgct					_	20
ctgggctgcc	tggttaaaga	ttatttcccg	gaaccagtca	ccgtgagctg	gaacagcggg		80
gcgctgacca	gcggcgtgca	tacctttccg	gcggtgctgc	aaagcagcgg	cctgtatagc		40
	ttgtgaccgt						00
gtgaaccata	aaccgagcaa	caccaaagtg	gataaaaaag	tggaaccgaa	aagc	6	54
<210> 284							
40335 601							

<211> 681

```
<212> DNA
<213> Homo sapiens
<400> 284
                                                                        60
caqqtqcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg
                                                                       120
agctgcaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc
                                                                       180
cetgggcagg gtctcgagtg gatgggcggc attattccga tttttggcac ggcgaactac
                                                                       240
gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgttggtct
                                                                       300
gatcagtctt atcattatta ttggcatcct tattttgatg tttggggcca aggcaccctg
                                                                       360
                                                                       420
qtqacqqtta qctcaqcqtc qaccaaaqqt ccaaqcqtqt ttccqctqqc tccqaqcaqc
                                                                       480
aaaaqcacca gcggcggcac ggctgccctg ggctgcctgg ttaaagatta tttcccggaa
                                                                       540
ccaqtcaccg tgagctggaa cagcggggcg ctgaccagcg gcgtgcatac ctttccggcg
                                                                       600
gtgctgcaaa gcagcggcct gtatagcctg agcagcgttg tgaccgtgcc gagcagcagc
                                                                       660
ttaggcactc agacctatat ttgcaacgtg aaccataaac cgagcaacac caaagtggat
                                                                       681
aaaaaagtgg aaccgaaaag c
<210> 285
<211> 654
<212> DNA
<213> Homo sapiens
<400> 285
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg
                                                                       60
aqctgcgcgg cctccggatt tacctttagc agctatgcga tgagctgggt gcgccaagcc
                                                                       120
cctgggaagg gtctcgagtg ggtgagcgcg attagcggta gcggcggcag cacctattat
                                                                       180
                                                                       240
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtcttatt
                                                                       300
ggttattttg atctttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa
                                                                       360
ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc
                                                                       420
                                                                       480
ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg
gcgctgacca gcggcgtgca tacctttccg gcggtgctgc aaagcagcgg cctgtatagc
                                                                       540
ctqaqcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac
                                                                       600
                                                                       654
gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagc
<210> 286
<211> 669
<212> DNA
<213> Homo sapiens
<400> 286
                                                                        60
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
                                                                       120
agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat
                                                                       180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat
                                                                       240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtcttact
                                                                       300
aattattttg attetattta ttatgateat tggggeeaag geaccetggt gaeggttage
                                                                       360
                                                                       420
tcagcgtcga ccaaaggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc
                                                                       480
ggcggcacgg ctgccctggg ctgcctggtt aaagattatt tcccggaacc agtcaccgtg
                                                                       540
aqctqqaaca qcqqqqcqct gaccagcgqc gtgcatacct ttccqqcqqt gctgcaaagc
```

ageggeetgt acetatattt eegaaaage	atagcctgag gcaacgtgaa	cagcgttgtg ccataaaccg	accgtgccga agcaacacca	gcagcagctt aagtggataa	aggcactcag aaaagtggaa	600 660 669
<210> 287 <211> 669 <212> DNA <213> Homo	sapiens					
agctgcaaag cctgggaagg tctccgagct cttcaatgga ggtggtggtt tcagcgtcga ggcggcacgg agctggaaca agcggcctgt	gttccggata gtctcgagtg ttcagggcca gcagcctgaa atgatcttat ccaaaggtcc ctgccctggg gcggggcgct atagcctgag	ttcctttacg gatgggcatt ggtgaccatt agcgagcgat	agctattgga atttatccgg agcgcggata acggccatgt tggggccaag ccgctggctc aaagattatt gtgcatacct accgtgccga	ttggctgggt gcgatagcga aaagcattag attattgcgc gcaccctggt cgagcagcaa tcccggaacc ttccggcggt gcagcagctt	tacccgttat caccgcgtat gcgtcttgtt gacggttagc aagcaccagc agtcaccgtg gctgcaaagc aggcactcag	120 180 240 300
<210> 288 <211> 672 <212> DNA <213> Homo	sapiens					
agctgcaaag cctgggaagg tctccgagct cttcaatgga acttatggtt agctcagcgt agcggcggca gtgagctgga agcagcggcc	gttccggata gtctcgagtg ttcagggcca gcagcctgaa atgatgatta cgaccaaagg cggctgccct acagcggggc tgtatagcct tttgcaacgt	cggcgcggaa ttcctttacg gatgggcatt ggtgaccatt agcgagcgat tcattttgat tccaagcgtg gggctgcctg gctgaccagc gagcagcgtt gaaccataaa	agctattgga atttatccgg agcgcggata acggccatgt tattggggcc tttccgctgg gttaaagatt ggcgtgcata gtgaccgtgc	ttggctgggt gcgatagcga aaagcattag attattgcgc aaggcaccct ctccgagcag atttcccgga cctttccggc cgagcagcag	gcgccagatg tacccgttat caccgcgtat gcgttatgtt ggtgacggtt caaaagcacc accagtcacc ggtgctgcaa cttaggcact	60 120 180 240 300 360 420 480 540 600 660 672
<210> 289 <211> 651 <212> DNA <213> Homo	sapiens				·	
		tggcgcggaa cacttttagc				60 120

cctgggcagg gtctcgagtg gcgcagaagt ttcagggccg atggaactga gcagcctgcg tatcttgatt attggggcca ccaagcgtgt ttccgctggc ggctgcctgg ttaaagatta ctgaccagcg gcgtgcatac agcagcgttg tgaccgtgcc aaccataaac cgagcaacac	ggtgaccatt tagcgaagat aggcaccetg tccgagcagc tttcccggaa ctttccggcg gagcagcagc	accgcggatg acggccgtgt gtgacggtta aaaagcacca ccagtcaccg gtgctgcaaa ttaggcactc	aaagcaccag attattgcgc gctcagcgtc gcggcggcac tgagctggaa gcagcggcct agacctatat	caccgcgtat gcgttctggt gaccaaaggt ggctgccctg cagcggggcg gtatagcctg ttgcaacgtg	180 240 300 360 420 480 540 600 651
<210> 290 <211> 687 <212> DNA <213> Homo sapiens					
<pre><400> 290 caggtgcaat tggttcagtc agctgcaaag cctccggagg cctgggcagg gtctcgagtg gcgcagaagt ttcaggccg atggaacta gcagcctgcg ggttatacta atgttatgga accetggtga cggttagctc agcagcaaaa gcaccagcgg ccggaaccag tcaccgtgag ccggcggtgc tgcaaagcag agcagcttag gcactcagac gtggataaaa aagtggaacc <210> 291 <211> 669 <212> DNA <213> Homo sapiens</pre>	cacttttagc gatgggcggc ggtgaccatt tagcgaagat tattcgtcct agcgtcgacc cggcacggct ctggaacagc cggcctgtat ctatatttgc	agctatgcga attattccga accgcggatg acggccgtgt ggtttttatc aaaggtccaa gccctgggct ggggcgctga agcctgagca	ttagctgggt tttttggcac aaagcaccag attattgcgc ttgattattg gcgtgtttcc gcctggttaa ccagcggcgt gcgttgtgac	gcgccaagcc ggcgaactac caccgcgtat gcgttatatt gggccaaggc gctggctccg agattatttc gcataccttt cgtgccgagc	60 120 180 240 300 360 420 480 540 600 660 687
<pre><400> 291 caggtgcaat tggttcagag agctgcaaag gttccggata cctgggaagg gtctcgagtg tctccgagct ttcagggcca cttcaatgga gcagcctgaa gcttatggtg atgatttta tcagcgtcga ccaaaggtcc ggcggcacgg ctgccetggg agctggaaca gcggggcgct agcggcctgt atagcctgag acctatattt gcaacgtgaa ccgaaaagc </pre> <pre><210> 292 <211> 678</pre>	ttcctttacg gatgggcatt ggtgaccatt agcgagcgat ttttgatgtt aagcgtgttt ctgcctggtt gaccagcggc cagcgttgtg	agctattgga atttatccgg agcgcggata acggccatgt tggggccaag ccgctggctc aaagattatt gtgcatacct accgtgccga	ttggctgggt gcgatagcga aaagcattag attattgcgc gcaccctggt cgagcagcaa tcccggaacc ttccggcggt gcagcagctt	gcgccagatg tacccgttat caccgcgtat gcgttttcgt gacggttagc aagcaccagc agtcaccgtg gctgcaaagc aggcactcag	60 120 180 240 300 360 420 480 540 660 669

<212> DNA <213> Homo sapiens				
<pre><400> 292 caggtgcaat tggttcagag cggc agctgcaaag cctccggata tacc cctgggcagg gtctcgagtg gatg gcgcagaagt ttcagggccg ggtg atggaactga gcagcctgcg tagc tggtctgatt atggtcagct tgtt acggttagct cagcgtcagc tgcc gtcaccagcg gctggaacag cggg gtcaccaga gctggaacag cggg ggcactcaga cctatatttg caac aaagtggaac cgaaaagc</pre>	etttacc agctattata- gggctgg attaacccga gaccatg acccgtgata gaagat acggccgtgt aagggt ggtgatattt aggtcca agcgtgttc ctgggc tgcctggtta ggcgctg accagcggcg ctgagc agcgttgtga	tgcactggt a tagcggcgg ccagcattag a ttattgcgc ggggccaagg cgctggctcc a agattattt tgcatacctt t	ccgccaagcc cacgaactac caccgcgtat gcgtattatg caccctggtg gagcagcaaa cccggaacca tccggcggtg cagcagctta agtggataaa	60 120 180 240 300 360 420 480 540 600 660 678
<210> 293 <211> 666 <212> DNA <213> Homo sapiens			· ·	
<pre><400> 293 caggtgcaat tggttcagag cggc agctgcaaag gttccggata ttcc cctgggaagg gtctcgagtg gatg tctccgagct ttcagggcca ggtg cttcaatgga gcagcctgaa agcg gttactgata ctgcttattt tgat gcgtcgacca aaggtccaag cgtg ggcacggctg ccctgggctg cctg tggaacagcg gggcgctgac cagc ggcctgtata gcctgagcag cgtt tatatttgca acgtgaacca taaa aaaagc</pre>	etttacg agctattgga gggcatt atttatccgg gaccatt agcgcggata gacgat acggccatgt tattgg ggccaaggca gttaccg ctggctccga ggttaaa gattatttcc ggcgtg catacctttc ggtgacc gtgccgagca	ttggctggt g gcgatagcga a aaagcattag a attattgcgc g ccctggtgac g gcagcaaaaag g cggaaccagt g cggcggtgct g gcagcttagg	gegecagatg taccegttat caccgcgtat gegttattat ggttagetea caccagegge caccgtgage geaaageage cactcagace	60 120 180 240 300 360 420 480 540 660 666
<210> 294 <211> 666 <212> DNA <213> Homo sapiens				
<400> 294 caggtgcaat tggttcagag cggc agctgcaaag gttccggata ttcc cctgggaagg gtctcgagtg gatg tctccgagct ttcagggcca ggtg cttcaatgga gcagcctgaa agcg tttgatggtt ctatttttat ggat gcgtcgacca aaggtccaag cgtg ggcacggctg ccctgggctg cctg	etttacg agctattgga ggcatt atttatccgg accatt agcgcggata agcgat acggccatgt ttttgg ggccaaggca etttccg ctggctccga	ttggctgggt g gcgatagcga t aaagcattag d attattgcgc g ccctggtgac g gcagcaaaag d	gegecagatg taccegttat caccgegtat gegteatgat ggttagetea caccagegge	60 120 180 240 300 360 420 480

tggaacagcg gggcgctgac ggcctgtata gcctgagcag tatatttgca acgtgaacca aaaagc	cgttgtgacc	gtgccgagca	gcagcttagg	cactcagacc	540 600 660 666
<210> 295 <211> 669 <212> DNA <213> Homo sapiens					
<400> 295 caggtgcaat tggttcagag agctgcaaag gttccggata cctgggaagg gtctcgagtg tctccgagct ttcagggcca cttcaatgga gcagcctgaa ggtcatcagt atgagtttt tcagcgtcga ccaaaggtcc ggcggcacgg ctgccctggg agctggaaca gcggggcgct agcggcctgt atagcctgag acctatattt gcaacgtgaa ccgaaaagc	ttcctttacg gatgggcatt ggtgaccatt agcgagcgat ttttgatttt aagcgtgttt ctgcctggtt gaccagcggc cagcgttgtg	agctattgga atttatccgg agcgcggata acggccatgt tggggccaag ccgctggctc aaagattatt gtgcatacct accgtgccga	ttggctgggt gcgatagcga aaagcattag attattgcgc gcaccctggt cgagcagcaa tcccggaacc ttccggcggt gcagcagctt	gcgccagatg tacccgttat caccgcgtat gcgttatgct gacggttagc aagcaccagc agtcaccgtg gctgcaaagc aggcactcag	60 120 180 240 300 360 420 480 540 600 660
<210> 296 <211> 614 <212> DNA <213> Homo sapiens					
<pre><400> 296 tgaaaattag ctgcaaaggt gccagatgcc tgggaagggt cccgttattc tccgagcttt ccgcgtatct tcaatggagc gtctttatgc tgatgctgat ttagctcagc gtcgaccaaa ccagcggcgg cacggctgcc ccgtgagctg gaacagcggg aaagcagcgg cctgtatagc ctcagaccta tatttgcaac</pre>	ctcgagtgga cagggccagg agcctgaaag atttattttg ggtccaagcg ctgggctgcc gcgctgacca ctgagcagcg	tgggcattat tgaccattag cgagcgatac attattgggg tgtttccgct tggttaaaga gcggcgtgca ttgtgaccgt	ttatccgggc cgcggataaa ggccatgtat ccaaggcacc ggctccgagc ttatttcccg tacctttccg	gatagcgata agcattagca tattgcgcgc ctggtgacgg agcaaaagca gaaccagtca gcggtgctgc agcttaggca	60 120 180 240 300 360 420 480 540
tggaaccgaa aagc	gtgaaccata	aaccgagcaa	caccaaagtg	gataaaaaag	600 614
<pre><ggaaccgaa <210="" aagc=""> 297 <211> 660 <212> DNA <213> Homo sapiens</ggaaccgaa></pre>	ģtgaaccata	aaccgagcaa	caccaaagtg	gataaaaaag	

```
cctgggcagg gtctcgagtg gatgggcggc attattccga tttttggcac gqcqaactac
                                                                       180
gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat
                                                                       240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtactaag
                                                                       300
tatgttggtt ctgaggatgt ttggggccaa ggcaccctgg tgacggttag ctcagcgtcg
                                                                       360
accaaaggtc caagcgtgtt tccgctggct ccgagcagca aaagcaccag cqqcqqcacg
                                                                       420
getgeectgg getgeetggt taaagattat tteeeggaae eagteaeegt gagetggaae
                                                                       480
agcggggcgc tgaccagcgg cgtgcatacc tttccggcgg tgctgcaaag cagcggcctg
                                                                       540
tatageetga geagegttgt gacegtgeeg ageageaget taggeactea gacetatatt
                                                                       600
tgcaacgtga accataaacc gagcaacacc aaagtggata aaaaagtgga accqaaaaqc
                                                                       660
<210> 298
<211> 660
<212> DNA
<213> Homo sapiens
<400> 298
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
                                                                       60
agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg
                                                                       120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat
                                                                       180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat
                                                                       240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatcgt
                                                                       300
tatcctcata tgtttgattt ttggggccaa ggcaccctgg tgacggttag ctcagcgtcg
                                                                       360
accaaaggtc caagcgtgtt tccgctggct ccgagcagca aaagcaccag cggcggcacg
                                                                       420
gctgccctgg gctgcctggt taaagattat ttcccggaac cagtcaccgt gagctggaac
                                                                       480
agcgggggcc tgaccagcgg cgtgcatacc tttccggcgg tgctgcaaag cagcggcctg
                                                                       540
tatagectga geagegttqt gaccqtqccq ageageaget taggeactea gacctatatt
                                                                       600
tgcaacgtga accataaacc gagcaacacc aaagtggata aaaaagtgga accgaaaagc
                                                                       660
<210> 299
<211> 666
<212> DNA
<213> Homo sapiens
<400> 299
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
                                                                        60
agetgeaaag gtteeggata tteetttaeg agetattgga ttggetgggt gegeeagatg
                                                                       120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat
                                                                       180
tetecgaget tteagggeea ggtgaceatt agegeggata aaageattag cacegegtat
                                                                       240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtcttttt
                                                                       300
gctggtcttg agctttattt tgattattgg ggccaaggca ccctggtgac ggttagctca
                                                                       360
gcgtcgacca aaggtccaag cgtgtttccg ctggctccga gcagcaaaag caccagcggc
                                                                       420
ggcacggctg ccctgggctg cctggttaaa gattatttcc cggaaccagt caccgtgagc
                                                                       480
tggaacagcg gggcgctgac cagcggcgtg catacettte cggcggtgct gcaaagcage
                                                                       540
ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc
                                                                       600
tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaccg
                                                                       660
                                                                       666
aaaagc
<210> 300
<211> 657
```

<212> DNA

<213> Homo sapiens

agctgcgcgg cctgggaagg gcggatagcg ctgcaaatga ttttttaata aaaggtccaa gccctgggct ggggcgctga agcctgagca	cctccggatt gtctcgagtg tgaaaggccg acagcctgcg tggattattg gcgtgtttcc gcctggttaa ccagcggcgt gcgttgtgac	tacctttagc ggtgagcgcg ttttaccatt tgcggaagat gggccaaggc gctggctccg agattatttc gcataccttt cgtgccgagc	agctatgcga attagcggta tcacgtgata acggccgtgt accctggtga agcagcaaaa ccggaaccag ccggcggtgc agcagcttag	cgggcggcag tgagctgggt gcggcggcag attcgaaaaa attattgcgc cggttagctc gcaccagcgg tcaccgtgag tgcaaagcag gcactcagac aagtggaacc	gcgccaagcc cacctattat caccctgtat gcgtggtggt agcgtcgacc cggcacggct ctggaacagc cggcctgtat ctatatttgc	60 120 180 240 300 360 420 480 540 600 657
<210> 301 <211> 663 <212> DNA <213> Homo	sapiens					
agctgcaaag cctgggcagg gcgcagaagt atggaactga attccttatc tcgaccaaag acggctgccc aacagcgggg ctgtatagcc	cctccggagg gtctcgagtg ttcagggccg gcagcctgcg atctttttga gtccaagcgt tgggctgcct cgctgaccag tgagcagcgt	cacttttagc gatgggcggc ggtgaccatt tagcgaagat ttattggggc gtttccgctg ggttaaagat cggcgtgcat tgtgaccgtg	agctatgcga attattccga accgcggatg acggccgtgt caaggcaccc gctccgagca tatttcccgg acctttccgg ccgagcagca	cgggcagcag ttagctgggt tttttggcac aaagcaccag attattgcgc tggtgacggt gcaaaagcac aaccagtcac cggtgctgca gcttaggcac ataaaaaagt	gcgccaagcc ggcgaactac caccgcgtat gcgtggttat tagctcagcg cagcggcggc cgtgagctgg aagcagcggc tcagacctat	60 120 180 240 300 360 420 480 540 660 663
<210> 302 <211> 669 <212> DNA <213> Homo	sapiens		·		٠.,	
agctgcaaag cctgggaagg tctccgagct cttcaatgga ggttttgagt tcagcgtcga ggcggcacgg agctggaaca	gttccggata gtctcgagtg ttcagggcca gcagcctgaa atgatcttct ccaaaggtcc ctgccctggg gcggggcgct	ttcctttacg gatgggcatt ggtgaccatt agcgagcgat ttttgataat aagcgtgttt ctgcctggtt gaccagcggc	agctattgga atttatccgg agcgcggata acggccatgt tggggccaag ccgctggctc aaagattatt gtgcatacct	cgggcgaaag ttggctgggt gcgatagcga aaagcattag attattgcgc gcaccctggt cgagcagcaa tcccggaacc ttccggcggt gcagcagctt	gcgccagatg tacccgttat caccgcgtat gcgttattat gacggttagc aagcaccagc agtcaccgtg gctgcaaagc	60 120 180 240 300 360 420 480 540

acctatatt ccgaaaagc	t gcaacgtga	a ccataaacc	g agcaacacc	a aagtggata	a aaaagtggaa	660 669
<210> 303						
<211> 657		•				
<212> DNA						
<213> Home	o sapiens					
<400> 303						
caggtgcaa	tggttcagtd	c tggcgcgga:	a gtgaaaaaa	c cgggcagca	g cgtgaaagtg	60
agorgonday	y culturgyay	, cacittag	c adctatoco:	a ttadctddd	t acacaaaaaa	120
cccgggcag	, grocegage	a gatgageta	attaaccco:	atagoggo	T Caccaachae	180
gogoagaagi	- cccayyycc	y ggtgaccat	a acceptoat:	a ccarcatta	T Caccacatat	240
acggaactg	z gcaycetyce	, Lagogaagai	c acooccoto	: attattocoo	acatattact	300
Lacattggt	. alyaliliti	, gggccaagg	c accctaataa	a coottaocto	- accetecases	360
accetagact	acctactte	gerggeree	g agcagcaaaa	gcaccagcg	g cggcacggct	420
qqqqcqctaa	. ccaacaacat	contactti	coggaacca	tcaccgtgag	g eggeaegget g etggaacage g eggeetgtat	480
agcctgagca	acattataac	: cataccasa	coggoggtge	tgcaaagcag	cggcctgtat ctatatttgc	540
aacgtgaacc	: ataaaccgag	caacaccaa	gtggataaaa	a aagtggaaco	gaaaagc	600 657
<210> 304			•			
<211> 654						
<212> DNA						
<213> Homo	sapiens					
<400> 304					•	
caggtgcaat	tggttcagtc	tggcgcggaa	gtgaaaaaac	cgggcagcag	cgtgaaagtg	60
-goog caaag	cccccggagg	Cacilliago	adctatdcda	ttagetgggt	GCGCCC22GCC	120
cctgggcagg	greecgageg	gatgagagag	attattccca	tttttaacea	aaaaaaataa	180
gegeagaagt	ricagggccg	ggtgaccatt	accocooato	aaaacaccaa	Caccacatat	240
acggaaccga	guaguutuuu	Laucuaadat	acaaccatat	attattacca	acat as as a	300
ggtccaacca	attattgggg	ccaaggcacc	ctggtgacgg	ttagctcagc	gtcgaccaaa	360
3322444	egeeeeegee	ggctccqaqc	aucaaaaaca	CCSGCGGCGG	cacaataaa	420
gcgctgacca	tggttaaaga gcggcgtgca	tacctttccc	gaaccagtca	ccgtgagctg	gaacagcggg	480
ctgagcagcg	ttgtgaccgt	accasacsac	acttacce	adageagegg	cctgtatagc	540
gtgaaccata	aaccgagcaa	caccaaagtg	gataaaaaag	tggaaccgaa	aagc	600 654
<210> 305			•			
<211> 666					•	•
<212> DNA						
<213> Homo	sapiens					
<400> 305						
caggtgcaat	tggttcagag	cggcgcggaa	gtgaaaaaac	cgggcgaaaq	cctgaaaatt	. 60
agorgeadag	gricciggata	LLCCTTTacq	agctattgga	ttaactaaat	acaccaaata	120
cccyyyaayy	greecegagtg	gatgggcatt	atttatecoo	acastaacas	tacccattat	180
ccccgagcc	LLCagggcca	ggtgaccatt	adcdcddata	aaagcattag	Caccacatat	240
cccaaryga	gcagcctgaa	agcgagcgat	acggccatgt	attattgcgc	gcgtctttat	300

```
cctgaggatc ttatttattt tgattattgg ggccaaggca ccctggtgac ggttagctca
                                                                       360
                                                                       420
gcgtcgacca aaggtccaag cgtgtttccg ctggctccga gcagcaaaag caccagcggc
ggcacggctg ccctgggctg cctggttaaa gattatttcc cggaaccagt caccgtqagc
                                                                       480
tggaacageg gggegetgae cageggegtg catacettte eggeggtget geaaageage
                                                                       540
qqcctqtata qcctqaqcaq cqttqtqacc qtqccqaqca qcaqcttaqq cactcaqacc
                                                                       600
                                                                       660
tatatttqca acgtgaacca taaaccgagc aacaccaaag tqgataaaaa aqtqqaaccq
                                                                       666
aaaagc
<210> 306
<211> 687
<212> DNA
<213> Homo sapiens
<400> 306
caggigeaat igeaacagic iggiceggge ciggigaaac egageeaaac ecigageeig
                                                                        60
acctqtgcga tttccggaga tagcgtgagc agcaacagcg cggcgtggaa ctqgattcgc
                                                                       120
cagteteetg ggegtggeet egagtggetg ggeegtaeet attategtag caaatggtat
                                                                       180
aacgattatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac
                                                                       240
cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg
                                                                       300
cgttggatga ctcctcctgg tcattattat ggttatactt ttgatgtttg gggccaaggc
                                                                       360
accetggtga eggttagete agegtegace aaaggteeaa gegtgtttee getggeteeg
                                                                       420
ageageaaaa geaceagegg eggeaegget geeetggget geetggttaa agattattte
                                                                       480
ccggaaccag tcaccgtgag ctggaacagc ggggcgctga ccagcggcgt gcataccttt
                                                                       540
ccggcggtgc tgcaaagcag cggcctgtat agcctgagca gcgttgtgac cgtqccgagc
                                                                       600
agcagottag gcactcagac ctatatttgo aacgtgaacc ataaaccgag caacaccaaa
                                                                       660
gtggataaaa aagtggaacc gaaaagc
                                                                       687
<210> 307
<211> 669
<212> DNA
<213> Homo sapiens
<400> 307
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
                                                                        60
agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg
                                                                       120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat
                                                                       180
tctccqaqct ttcaqqqcca ggtqaccatt aqcqcqqata aaaqcattaq caccqcqtat
                                                                       240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcqtcttcqt
                                                                       300
gttcatgatt atgctatgta ttttgatctt tggggccaag gcaccctggt gacggttagc
                                                                       360
tcagcgtcga ccaaaggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc
                                                                       420
ggcqqcacqq ctgcctgqq ctgcctqqtt aaaqattatt tcccqqaacc aqtcaccqtq
                                                                       480
agctggaaca geggggeget gaccagegge gtgcatacet tteeggeggt getgcaaage
                                                                       540
aggggcctgt atagcctgag cagggttgtg accqtqccga gcagcagctt aggcactcag
                                                                       600
acctatattt qcaacqtqaa ccataaaccq aqcaacacca aaqtqqataa aaaaqtqqaa
                                                                       660
ccqaaaaqc
                                                                       669
<210> 308
<211> 672
<212> DNA
<213> Homo sapiens
```

```
<400> 308
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
                                                                        60
agctgcaaag gttccggata ttcctttacg agctattgga ttggctgggt gcgccagatg
                                                                       120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat
                                                                       180
tctccqaqct ttcaqqqcca qqtqaccatt aqcqcqqata aaaqcattaq caccqcqtat
                                                                       240
cttcaatgga gcagcctqaa aqcgaqcqat acqqccatqt attattqcqc qcqttttqtt
                                                                       300
tettataatg gttetgttee ttattttgat tattggggee aaggeaccet ggtgaeggtt
                                                                       360
ageteagegt egaceaaagg tecaagegtg ttteegetgg eteegageag caaaageace
                                                                       420
ageggeggca eggetgeeet gggetgeetg gttaaagatt attteeegga accagteace
                                                                       480
gtgagctgga acagcggggc gctgaccagc ggcgtgcata cctttccggc ggtgctgcaa
                                                                       540
ageageggee tgtatageet gageagegtt gtgaeegtge egageageag ettaggeaet
                                                                       600
cagacctata tttgcaacgt gaaccataaa ccgagcaaca ccaaagtgga taaaaaagtg
                                                                       660
qaaccqaaaa qc
                                                                       672
<210> 309
<211> 666
<212> DNA
<213> Homo sapiens
<400> 309
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
                                                                        60
agctgcaaag gttccggata ttcctttacg agctattgga ttggctgqqt gcqccagatg
                                                                       120
cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga tacccgttat
                                                                       180
tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat
                                                                       240
cttcaatgga gcagcctgaa agcgagcgat accgcccatgt attattgcgc gcgtattatt
                                                                       300
ggtgattatg ttatttttt tgatgtttgg ggccaaggca ccctggtgac ggttagctca
                                                                       360
gcqtcqacca aaggtccaaq cqtqtttccq ctqqctccqa qcaqcaaaaq caccaqcqqc
                                                                       420
ggcacggctg ccctgggctg cctggttaaa gattatttcc cggaaccagt caccgtgagc
                                                                       480
tggaacagcg gggcgctgac cagcggcgtg catacettte cggcggtgct gcaaaqcage
                                                                       540
ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc
                                                                       600
tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaccg
                                                                       660
aaaagc
                                                                       666
<210> 310
<211> 609
<212> DNA
<213> Homo sapiens
<400> 310
attagctgca aaggttccgg atattccttt acgagctatt ggattggctg ggtgcgccag
                                                                        60
atgcctggga agggtctcga gtggatgggc attatttatc cgggcgatag cgatacccgt
                                                                       120
tatteteega gettteaggg ceaggtgace attagegegg ataaaageat tageacegeg
                                                                       180
tatetteaat ggageageet gaaagegage gataeggeea tqtattattg egegegtett
                                                                       240
tttacttatc cttttcttta ttttgatgtt tggggccaag gcaccctggt gacggttagc
                                                                       300
tcagcqtcqa ccaaaqqtcc aaqcqtqttt ccqctqqctc cqaqcaqcaa aaqcaccaqc
                                                                       360
ggcggcacgg ctgccctggg ctgcctggtt aaagattatt tcccggaacc agtcaccgtg
                                                                       420
agctggaaca geggggeget gaccagegge gtgcatacet tteeggeggt getgeaaage
                                                                       480
ageggeetgt atageetgag eagegttgtg acegtgeega geageagett aggeaeteag
                                                                       540
acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa
                                                                       600
```

ccgaaaagc	609
<210> 311	
<211> 666	
<212> DNA <213> Homo sapiens	·
(213) Homo Saptens	
<400> 311	
	ggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60
	tacg agetattgga ttggetgggt gegecagatg 120 catt atttateegg gegatagega taccegttat 180
	catt atttatccgg gcgatagcga tacccgttat 180 catt agcgcggata aaagcattag caccgcgtat 240
	cgat acggccatgt attattgcgc gcgtattctt 300
	tigg ggccaaggca ccctggigac ggitagcica 360
	tccg ctggctccga gcagcaaaag caccagcggc 420
	taaa gattatttcc cggaaccagt caccgtgagc 480
tggaacagcg gggcgctgac cagcgg	egtg catacettte eggeggtget geaaageage 540 gace gtgeegagea geagettagg cacteagace 600
tatatttgca acgtgaacca taaacc	gacc gtgccgagca gcagcttagg cactcagacc 600 gagc aacaccaaag tggataaaaa agtggaaccg 660
aaaagc	666
<210> 312	
<211> 645	
<212> DNA <213> Homo sapiens	
(213) Homo Baptens	•
<400> 312	
gatatogoac tgacccagoc agotto	agtg agcggctcac caggtcagag cattaccatc 60
gatategeae tgacecagee agette tegtgtaegg gtactageag egatgt	gggc ggctataact atgtgagctg gtaccagcag 120
gatategeae tgacecagee agette tegtgtaegg gtactageag egatgt cateceggga aggegeegaa actgat	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180
gatategeae tgacecagee agette tegtgtaegg gtactageag egatgt cateceggga aggegeegaa actgate ageaacegtt ttageggate caaaag	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240
gatategeae tgacecagee agette tegtgtaegg gtactageag egatgt cateceggga aggegeegaa actgate ageaaeegtt ttageggate caaaage caageggaag aegaagegga ttatta	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240
gatatcgcac tgacccagcc agetted tegtgtacgg gtactagcag egatgted cateceggga aggegeegaa actgated ageaacegtt ttageggate caaaagggaag acgaagegga ttattagetgtteege egageagega agaatteetgtteege egageagega agaatte	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctatg actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420
gatatcgcac tgacccagcc agetted tegtgtacgg gtactagcag egatgte cateceggga aggegeegaa actgate ageaacegtt ttageggate caaaagggaag acgaagegga ttattagttteggeggeg geacgaagtt aacegteetgtteege egageagega agaatteagegactttt ateegggage egtgacag	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctatg actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480
gatatcgcac tgacccagcc agcttcd tcgtgtacgg gtactagcag cgatgtc catcccggga aggcgccgaa actgatc agcaaccgtt ttagcggatc caaaagg caagcggaag acgaagcgga ttattad tttggcggcg gcacgaagtt aaccgtd ctgtttccgc cgagcagcga agaattc agcgactttt atccgggagc cgtgaca gcgggagtgg agaccaccac accctc	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctatg actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540
gatategeae tgacecagee agetted tegtgtaegg gtactageag egatgte cateceggga aggegeegaa actgate ageaacegtt ttageggae teattageggaag acgaagegga ttattagetteege egageagega agaatte agegaetttt ateegggage egtgaegeggagtgg agaceaceae accetegtatetgagee tgacegeeggagegeggagtgg agaceaceae accetegtatetgagee tgacegeeggagegegggagtgg	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctat actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540 gaag tcccacagaa gctacagctg ccaggtcacg 600
gatatcgcac tgacccagcc agcttcd tcgtgtacgg gtactagcag cgatgtc catcccggga aggcgccgaa actgatc agcaaccgtt ttagcggatc caaaagg caagcggaag acgaagcgga ttattad tttggcggcg gcacgaagtt aaccgtd ctgtttccgc cgagcagcga agaattc agcgactttt atccgggagc cgtgaca gcgggagtgg agaccaccac accctc	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctat actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540 gaag tcccacagaa gctacagctg ccaggtcacg 600
gatategeae tgacecagee agette tegtgtaegg gtactageag egatge cateceggga aggegeegaa actgate ageaacegtt ttageggate caaaagg caageggaag acgaagegga ttatta tttggeggeg geacgaagtt aacegte etgtteege egageagega agaatte agegaetttt ateegggage egtgae gegggagtgg agaceaceae accete tatetgagee tgaegeetga geagtge catgagggga geacegtgga aaaaace <210> 313	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctat actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540 gaag tcccacagaa gctacagctg ccaggtcacg 600
gatategeae tgacecagee agette tegtgtaegg gtactageag egatge cateceggga aggegeegaa actgate ageaacegtt ttageggate caaaagg caageggaag acgaagegga ttatta tttggeggeg geacgaagtt aacegte etgtteege egageagega agaatte agegaetttt ateegggage egtgae gegggagtgg agaceaceae accete tatetgagee tgaegeetga geagtgg catgagggga geacegtgga aaaaace <210> 313 <211> 645	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctat actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540 gaag tcccacagaa gctacagctg ccaggtcacg 600
gatategeae tgacecagee agetted tegtgtaegg gtactageag egatgte catecegga aggegeegaa actgate ageaacegtt ttageggate caaaagg acaacegtt ttageggate caaaagg acaaggga geacgaagtt aacegte etgtteege egageagega agaatte ageggaettt ateegggage egtgae gegggagtgg agaceaceae acceteg eatgaggga geacegtga aaaaace eatgaggga geacegtga aaaaace eatgaggga geacegtgga aaaaace eatgaggga geacegtgga aaaaace eatgaggga egtgae eatgaggga geacegtgga aaaaace eatgaggga geacegtgga aaaaace eatgaggga eatgaggagga eatgaggagagga	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctat actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540 gaag tcccacagaa gctacagctg ccaggtcacg 600
gatategeae tgacecagee agette tegtgtaegg gtactageag egatge cateceggga aggegeegaa actgate ageaacegtt ttageggate caaaagg caageggaag acgaagegga ttatta tttggeggeg geacgaagtt aacegte etgtteege egageagega agaatte agegaetttt ateegggage egtgae gegggagtgg agaceaceae accete tatetgagee tgaegeetga geagtgg catgagggga geacegtgga aaaaace <210> 313 <211> 645	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctat actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540 gaag tcccacagaa gctacagctg ccaggtcacg 600
gatategeae tgacecagee agetted tegtgtaegg gtactageag egatgte catecegga aggegeegaa actgate ageaacegtt ttageggate caaaagg acaacegtt ttageggate caaaagg acaaggga geacgaagtt aacegte etgtteege egageagega agaatte ageggaettt ateegggage egtgae gegggagtgg agaceaceae acceteg eatgaggga geacegtga aaaaace eatgaggga geacegtga aaaaace eatgaggga geacegtgga aaaaace eatgaggga geacegtgga aaaaace eatgaggga egtgae eatgaggga geacegtgga aaaaace eatgaggga geacegtgga aaaaace eatgaggga eatgaggagga eatgaggagagga	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctat actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540 gaag tcccacagaa gctacagctg ccaggtcacg 600
gatategeac tgacecagec agetter tegtgtaegg gtactageag egatgte cateceggga aggegeegaa actgate ageaacegtt ttageggate caaaagg ttageggegg geaegaagtt aacegte etgtteege egageagega agaatte agegaettt ateegggage egtgae gegggagtgg agaceaceae accete tatetgagee tgaegeetga geagtge catgagggga geaeegtgga aaaaace <210> 313 <211> 645 <212> DNA <213> Homo sapiens	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctatg actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540 gaag tcccacagaa gctacagctg ccaggtcacg 600 cgtt gcgccgactg aggcc aggca aggca 645 agtg agcggtcac caggtcagag cattaccatc 60
gatategeae tgacecagee agettee tegtgtaegg gtactageag egatgte cateceggga aggegeegaa actgate ageaacegtt ttageggate caaaage caageggaag acgaagegga ttatta tttggeggeg geacgaagtt aacegte ctgttteege egageagega agaatte agegaetttt ateegggage egtgae gegggagtgg agaceaceae accetee tatetgagee tgacgeetga geagtge catgagggga geacegtgga aaaaace <210> 313 <211> 645 <212> DNA <213> Homo sapiens <400> 313 gatategeae tgacecagee agettee tegtgtaegg gtactageag egatge	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctatg actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540 gaag tcccacagaa gctacagctg ccaggtcacg 600 cgtt gcgccgactg aggcc aggca aggcgcacc caggtcaca 645 aggg agcggctcac caggtcagag cattaccatc 60 gggc ggctataact atgtgagctg gtaccagcag 120
gatategeae tgacecagee agettee tegtgtaegg gtactageag egatgte cateceggga aggegeegaa actgate ageaacegtt ttageggate caaaagg caageggaag acgaagegga ttatta tttggeggeg geacgaagtt aacegte ctgttteege egageagega agaatte agegaetttt ateegggage egtgae gegggagtgg agaceaceae accetee tatetgagee tgacgeetga geagtge catgagggga geacegtgga aaaaace <210> 313 <211> 645 <212> DNA <213> Homo sapiens <400> 313 gatategeae tgacecagee agettee tegtgtaegg aggegegaa agettee tegtgtaegg aggegegaa actgatee cateceggga aggegeegaa actgatee	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctatg actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540 gaag tcccacagaa gctacagctg ccaggtcacg 600 cgtt gcgccgactg aggcc aggca ggctataact atgtgagctg gtaccagcag 645 gagt ggctgaact accagctg cagataccatc 60 gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180
gatategeae tgacecagee agettee tegtgtaegg gtactageag egatgte cateceggga aggegeegaa actgate ageaacegtt ttageggate caaaage caageggaag acgaagegga ttatta tttggeggeg geacgaagtt aacegte ctgttteege egageagega agaatte agegaetttt ateegggage egtgae gegggagtgg agaceaceae accetee tatetgagee tgacgeetga geagtge catgagggga geacegtgga aaaaaae <210> 313 <211> 645 <212> DNA <213> Homo sapiens <400> 313 gatategeae tgacecagee agettee tegtgtaegg gtactageag egatge cateeggga aggegeegaa actgate ageaacegtt ttageggate caaaage	gggc ggctataact atgtgagctg gtaccagcag 120 gatt tatgatgtga gcaaccgtcc ctcaggcgtg 180 cggc aacaccgcga gcctgaccat tagcggcctg 240 ttgc cagagctatg actatcagca gtttactgtg 300 tctt ggccagccga aagccgcacc gagtgtgacg 360 gcag gcgaacaaag cgaccctggt gtgcctgatt 420 agtg gcctggaagg cagatagcag ccccgtcaag 480 caaa caaagcaaca acaagtacgc ggccagcagc 540 gaag tcccacagaa gctacagctg ccaggtcacg 600 cgtt gcgccgactg aggcc aggca aggcgcacc caggtcaca 645 aggg agcggctcac caggtcagag cattaccatc 60 gggc ggctataact atgtgagctg gtaccagcag 120

ctgtttccgc agcgactttt gcgggagtgg tatctgagcc	cgagcagcga atccgggagc agaccaccac tgacgcctga	aaccgttctt agaattgcag cgtgacagtg accetccaaa gcagtggaag aaaaaccgtt	gcgaacaaag gcctggaagg caaagcaaca tcccacagaa	cgaccctggt cagatagcag acaagtacgc gctacagctg	gtgcctgatt ccccgtcaag ggccagcagc	360 420 480 540 600 645
<210> 314 <211> 645 <212> DNA <213> Homo	sapiens					
tcgtgtacgg catcccggga agcaaccgtt caagcggaag tttggcggcg ctgtttccgc agcgactttt gcgggagtgg tatctgagcc	gtactagcag aggcgccgaa ttagcggatc acgaagcgga gcacgaagtt cgagcagcga atccgggagc agaccaccac tgacgcctga	agcttcagtg cgatgtgggc actgatgatt caaaagcggc ttattattgc aaccgttctt agaattgcag cgtgacagtg accctccaaa gcagtggaag aaaaaccgtt	ggctataact tatgatgtga aacaccgcga cagagctatg ggccagccga gcgaacaaag gcctggaagg caaagcaaca tcccacagaa	atgtgagctg gcaaccgtcc gcctgaccat actttcttcg aagccgcacc cgaccctggt cagatagcag acaagtacgc gctacagctg	gtaccagcag ctcaggcgtg tagcggcctg ttttctgtg gagtgtgacg gtgcctgatt ccccgtcaag	60 120 180 240 300 360 420 480 540 600 645
<210> 315 <211> 638 <212> DNA <213> Homo	sapiens					
tcgtgtacgg catcccggga agcaaccgtt caagcggaag tttggeggeg ctgtttccgc agcgactttt gcgggagtgg tatctgagcc	gtactagcag aggcgccgaa ttagcggatc acgaagcgga gcacgaagtt cgagcagcga atccgggagc agaccaccac tgacgcctga	agcttcagtg cgatgtgggc actgatgatt caaaagcggc ttattattgc aaccgttctt agaattgcag cgtgacagtg accctccaaa gcagtggaag aaaaaccgtt	ggctataact tatgatgtga aacaccgcga cagagctatg ggccagccga gcgaacaaaag gcctggaagg caaagcaaca tcccacagaa	atgtgagctg gcaaccgtcc gcctgaccat actttattaa aagccgcacc cgaccctggt cagatagcag acaagtacgc	gtaccagcag ctcaggcgtg tagcggcctg tgttattgtg gagtgtgacg gtgcctgatt ccccgtcaag ggccagcagc	60 120 180 240 300 360 420 480 540 600 638
<210> 316 <211> 645 <212> DNA <213> Homo <400> 316	sapiens					
gatategeae	tgacccagcc	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60

```
120
tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg
                                                                      180
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
                                                                      240
caageggaag acgaagegga ttattattgc cagagetatg actttgttcg ttttatggtg
                                                                      300
tttggcggcg gcacgaagtt aaccgttctt ggccagccga aagccgcacc gagtgtgacg
                                                                      360
ctgtttccgc cgagcagcga agaattgcag gcgaacaaag cgaccctggt gtgcctgatt
                                                                      420
agcgactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag
                                                                      480
                                                                      540
gegggagtgg agaccaccac accetecaaa caaagcaaca acaagtacge ggccagcage
                                                                      600
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg
                                                                       645
catgagggga gcaccgtgga aaaaaccgtt gcgccgactg aggcc
<210> 317
<211> 638
<212> DNA
<213> Homo sapiens
<400> 317
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc
                                                                        60
tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag
                                                                       120
                                                                      180
cateceggga aggegeegaa actgatgatt tatgatgtga geaacegtee etcaggegtg
aqcaaccqtt ttaqcqqatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
                                                                      240
caagcggaag acgaagcgga ttattattgc cagagctatg acttttataa gtttaatgtg
                                                                      300
                                                                      360
tttggcggcg gcacgaagtt aaccgttctt ggccagccga aagccgcacc gagtgtgacg
                                                                       420
ctqtttccqc cqaqcaqcqa agaattgcag gcgaacaaag cgaccctggt gtgcctgatt
agcqactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag
                                                                       480
gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc
                                                                       540
                                                                       600
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg
catgagggga gcaccgtgga aaaaaccgtt gcgccgac
                                                                       638
<210> 318
<211> 638
<212> DNA
<213> Homo sapiens
<400> 318
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc
                                                                        60
tcqtqtacgg qtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag
                                                                       120
catcccqqqa aqqcqccqaa actqatqatt tatgatqtqa qcaaccqtcc ctcaggcgtg
                                                                       180
                                                                       240
agcaaccqtt ttaqcqqatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
                                                                       300
caaqcqqaaq acqaaqcqqa ttattattgc cagagctatg actttcgtcg tttttctgtg
tttggeggeg geacgaagtt aaccgttett ggecageega aageegeace gagtgtgaeg
                                                                       360
                                                                       420
ctgtttccgc cgagcagcga agaattgcag gcgaacaaag cgaccctggt gtgcctgatt
agcgactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag
                                                                       480
gegggagtgg agaccaccac accetecaaa caaagcaaca acaagtacge ggccaqcaqe
                                                                       540
                                                                       600
tatctqaqcc tqacqcctqa qcaqtqqaaq tcccacaqaa gctacagctg ccaggtcacg
catgagggga gcaccgtgga aaaaaccgtt gcgccgac
                                                                       638
<210> 319
<211> 642
<212> DNA
```

<213> Homo sapiens <400> 319 qatateqtqc tqacccaqcc qccttcaqtq agtqqcgcac caggtcagcq tqtqaccatc 60 tcgtgtagcg gcagcagcag caacattggc agcaactatg tgagctggta ccaqcagttg 120 cccqqqacqq cqccqaaact qctqatttat gataacaacc agcqtccctc aqqcqtqccq 180 qatcqtttta qcqqatccaa aaqcqqcacc aqcqcqaqcc ttqcqattac qqqcctqcaa 240 300 agegaagaeg aageggatta ttattgeeag ageegtgaet ttaategtgg teetgtgttt 360 ggeggeggca egaagttaac egttettgge cageegaaag eegcacegag tgtgaegetg 420 tttccgccga gcagcgaaga attgcaggcg aacaaagcga ccctggtgtg cctgattagc gacttttatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480 540 ggagtggaga ccaccacac ctccaaacaa agcaacaaca agtacgcggc cagcagctat ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600 642 gaggggagca ccgtggaaaa aaccgttgcg ccgactgagg cc <210> 320 <211> 639 <212> DNA <213> Homo sapiens <400> 320 60 gatategtge tgacecagee geetteagtg agtggegeae caggteageg tgtgaceate togtgtagcg gcagcagcag caacattggc agcaactatg tgagctggta ccagcagttg 120 180 cccqqqacqq cqccqaaact qctqatttat gataacaacc aqcqtccctc agqcqtqccq qateqtttta qeggatecaa aageggeaec agegegagec ttgegattac gggeetgeaa 240 agcgaagacg aagcggatta ttattgccag agctatgacc agcgtaagtg ggtgtttggc 300 360 ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt ceqecqaqca qegaaqaatt qeaqqeqaac aaaqeqacce tggtgtgcct gattagegac 420 ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480 qtqqaqacca ccacacctc caaacaaaqc aacaacaaqt acqcqqccag cagctatctg 5.40 agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600 639 gggagcaccg tggaaaaaac cgttgcgccg actgaggcc <210> 321 <211> 672 <212> DNA <213> Homo sapiens <400> 321 60 gatateqtqc tgacceagag eeeggegace etgageetgt eteegggega aegtgegace 120 ctgagetgea gagegageea gagegtgage ageagetate tggegtggta ceageagaaa 180 ccaggtcaag caccgcgtct attaatttat ggcgcgagca gccgtgcaac tggggtcccg gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240 cctgaagact ttgcgactta ttattgccag cagctttatg gtacttctgt tacctttggc 300 360 cagggtacga aagttgaaat taaacgtacg gtggctgctc cgagcgtgtt tatttttccg ccgagcgatq aacaactgaa aagcggcacg gcgagcgtgg tgtgcctgct gaacaacttt 420 tatecgegtg aagegaaagt teagtggaaa gtagacaaeg egetgeaaag eggeaaeage 480 540 caggaaagcg tgaccgaaca ggatagcaaa gatagcacct attctctgag cagcaccctg 600 accetgagea aageggatta tgaaaaacat aaagtgtatg egtgegaagt gaeeeateaa 660 ggtctgagca gcccggtgac taaatctttt aatcgtggcg aggcctgata agcatgcgta

ggagaaata aa	672
<210> 322 <211> 642 <212> DNA <213> Homo sapiens	
<pre><400> 322 gatatcgtgc tgacccagcc gccttcagtg agtggcgcac caggtcagcg tgtgaccatc tcgtgtagcg gcagcagcag caacattggc agcaactatg tgagctggta ccagcagttg cccgggacgg cgccgaaact gctgatttat gataacaacc agcgtccctc aggcgtgccg gatcgttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa agcgaagacg aagcggatta ttattgccag agctatgacg gttttaagac tcatgtgtt ggcggcgca cgaagttaac cgttcttggc cagccgaaag ccgcaccgag tgtgacgctg ttccgccag gcagcgaaga attgcaggcg acaaagcga ccctggtgtg cctgattagc gacttttatc cgggagccgt gacagtggcc tggaaggcag atagcagcc cgtcaaggcg</pre>	60 120 180 240 300 360 420 480 540
ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat gaggggagca ccgtggaaaa aaccgttgcg ccgactgagg cc	600 642
<210> 323 <211> 633 <212> DNA <213> Homo sapiens	
qatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc tcgtgtagcg gcgatgcgct gggcgataaa tacgcgagct ggtaccagca gaaacccggg caggcgccag ttctggtgat ttatgatgat tctgaccgtc cctcaggcat cccggaacgc tttagcggat ccaacacgcg cagacaccgc accatgacca ttagcggat ccaacacgcg attattattg ccagagctat gactattct ttcttgtgtt tggcggcgc accagagctata ccgttcttgg ccagccgaaa gccgcaccga gtgtgacgct gttccgccg agcagcgaa aattgcaggc gaacaaagcg accctggtgt gcctgattag cgactttat ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcggaccgaccgtaggaaa aaaccgttgc gccgactgag gcc	60 120 180 240 300 360 420 480 540 600 633
<210> 324 <211> 633 <212> DNA <213> Homo sapiens	
<pre><400> 324 gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc tcgtgtagcg gcgatgcgct gggcgataaa tacgcgagct ggtaccagca gaaacccggg caggcgccag ttctggtgat ttatgatgat tctgaccgtc cctcaggcat cccggaacgc tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa gacgaagcgg attattattg ccagagctat gactttaatt ttcatgtgtt tggcggcggc acgaagttaa ccgttcttgg ccagccgaaa gccgcaccga gtgtgacgct gtttccgccg</pre>	60 120 180 240 300 360

agcagcgaag aattgcaggc gaacaaagcg accetggtgt gcctgattag cgacttttat ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag accaccaca cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaggggagc accgtggaaa aaaccgttgc gccgactgag gcc	420 480 540 600 633
<210> 325 <211> 648 <212> DNA <213> Homo sapiens	
<pre><400> 325 gatategeac tgacccagec agetteagtg ageggeteac caggteagag cattaceate tegtgtacgg gtactageag egatgtggge ggetataact atgtgagetg gtaccageag cateceggga ageggeegaa actgatgatt tatgatgtga geaacegtee etcaggegtg ageaacegtt ttageggate caaaagegge aacacegega geetgaceat tageggeetg caageggaag acgaagegga ttattattge cagagetatg acatgattge tegttateet gtgtttggeg geggeacgaa gttaacegtt ettggeeage egaaageege acegagtgtg acgetgtte egeegageag egaagaattg caggegaaca aagegaecet ggtgtgeetg attagegaet tttateeggg ageegtgaea gtggeetgga aggeagatag eageeegte aaggegggag tggagaceae cacaceetee aaacaaagea acaacaagta egeggeeag acgeatgagg ggageacegt ggaaaaaace gttgeeega etgaggee</pre>	60 120 180 240 300 360 420 480 540 600 648
<210> 326 <211> 639 <212> DNA <213> Homo sapiens	
<pre><400> 326 gatatcgaac tgacccagcc tcgtgtagcg gcgatgcgct caggcgcag ttctggtgat tttagcggat ccaacagcgg gacgaagacgg attattattg ggcggcacag agttaaccgt tcgccgagca gcgaagaatt tctggcag agttaaccgt tcttggcag agttaaccgt gacatcatc tcttggcag accetgacca ttagcggaa gacgaagcgg attattattg ggcggcacag agttaaccgt tcttggcag gcgaagaatt ccgccgagca gcgaagaatt tcttggcag agtggcgaac agtggcggaac ttttatccgg gacgcgtgac agtggcggaac gtggagacca ccacaccctc agcctgacgc ttggaaaaaac ggagccaga gaagtcccac agaagcac agcagcagca ccacaccctc agcctgacgc ttggaaaaaac ggagccaca agaagtaca agaagcacc agcagcacca tggaaaaac gaagccaca agaagcacca gcgaccagac agcagcacca agaagcacca agaagcacca gcgccagac accacacagc accacacaccaccacacaca</pre>	60 120 180 240 300 360 420 480 540 600 639
<210> 327 <211> 639 <212> DNA <213> Homo sapiens	
<400> 327 gatatcgtgc tgacccagcc gccttcagtg agtggcgcac caggtcagcg tgtgaccatc tcgtgtagcg gcagcagcag caacattggc agcaactatg tgagctggta ccagcagttg	60 120

```
cccgggacgg cgccgaaact gctgatttat gataacaacc agcgtccctc aggcgtgccg
                                                                       180
                                                                       240
gategtttta geggatecaa aageggeace agegegagee ttgegattae gggeetgeaa
aqcgaagacg aagcggatta ttattgccag agctgggacc ttgagcctta tgtgtttggc
                                                                       300
ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacqctqttt
                                                                       360
ccqccqaqca qcgaaqaatt gcaggcqaac aaagcgaccc tggtgtgcct gattagcgac
                                                                       420
ttttatccqq qaqccqtqac aqtqqcctqq aaqqcaqata gcaqccccqt caaqqcqqqa
                                                                       480
                                                                       540
qtqqaqacca ccacaccete caaacaaage aacaacaagt acgeggeeag cagetatetg
                                                                       600
agectgacge ctgagcagtg gaagteecac agaagetaca getgeeaggt caegeatgag
                                                                       639
gggagcaccg tggaaaaaac cgttgcgccg actgaggcc
<210> 328
<211> 645
<212> DNA
<213> Homo sapiens
<400> 328
qatatcqcac tqacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc
                                                                        60
tcqtqtacqq qtactaqcaq cqatqtqgqc qqctataact atqtqaqctq gtaccaqcaq
                                                                       120
                                                                       180
catcccqqqa aggcqccqaa actgatqatt tatqatqtqa gcaaccgtcc ctcaggcqtq
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
                                                                       240
                                                                       300
caageggaag aegaagegga ttattattge cagagetatg aegttettga ttetgaggtg
tttqqcqqcq qcacqaagtt aaccgttctt ggccagccga aagccgcacc gagtgtgacg
                                                                       360
                                                                       420
ctqtttccgc cgagcagcga agaattgcag gcgaacaaag cgaccctggt gtgcctgatt
agcgactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag
                                                                       480
gegggagtgg agaceaceae accetecaaa caaageaaca acaagtaege ggeeaqeage
                                                                       540
tatctgagec tgacgectga geagtggaag teccacagaa getacagetg ecaggteacg
                                                                       600
catgagggga gcaccgtgga aaaaaccgtt gcgccgactg aggcc
                                                                       645
<210> 329
<211> 648
<212> DNA
<213> Homo sapiens
<400> 329
qatatcqcac tqacccaqcc aqcttcaqtq aqcqqctcac caqqtcaqaq cattaccatc
                                                                        60
tegtgtacgg gtactagcag egatgtggge ggetataact atgtgagetg gtaccagcag
                                                                       120
                                                                       180
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg
                                                                       240
agcaaccqtt ttaqcqqatc caaaaqcqqc aacaccqcqa gcctqaccat taqcqqcctq
                                                                       300
caageggaag acgaagegga ttattattge cagagetatg accettetea teettetaag
gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg
                                                                       360
acgetgttte egeegageag egaagaattg eaggegaaca aagegaeeet ggtgtgeetg
                                                                       420
attagcgact tttatccggg agccgtgaca gtggcctgga aggcagatag cagcccgtc
                                                                       480
aaggegggag tggagaccac cacaccctcc aaacaaagca acaacaagta cgcggccagc
                                                                       540
agetatetga geetgacgee tgageagtgg aagteecaca gaagetacag etgeeaggte
                                                                       600
acqcatqaqq qqaqcaccqt qqaaaaaacc gttqcqccqa ctqaqqcc
                                                                       648
<210> 330
<211> 642
<212> DNA
```

<213> Homo sapiens

tcgtgtacgg catcccggga agcaaccgtt caagcggaag ggcggcggca tttccgccga gacttttatc ggagtggaga ctgagcctga	gtactagcag aggcgccgaa ttagcggatc acgaagcgga cgaagttaac gcagcgaaga cgggagccgt ccaccacacc	cgatgtgggc actgatgatt caaaagcggc ttattattgc cgttcttggc attgcaggcg gacagtggcc ctccaaacaa gtggaagtcc	ggctataact tatgatgtga aacaccgcga cagagctatg cagccgaaag aacaaagcga tggaaggcag agcaacaaca cacagaagct	caggtcagag atgtgagctg gcaaccgtcc gcctgaccat acgatatgca ccgcaccgag ccctggtgtg atagcagccc agtacgcggc acagctgcca cc	gtaccagcag ctcaggcgtg tagcggcctg gtttgtgttt tgtgacgctg cctgattagc cgtcaaggcg cagcagctat	60 120 180 240 300 360 420 480 540 600 642
<210> 331 <211> 645 <212> DNA <213> Homo	sapiens					
tcgtgtacgg catcccggga agcaaccgtt caagcggaag tttggcggcg ctgtttccgc agcgactttt gcgggagtgg tatctgagcc	gtactagcag aggcgccgaa ttagcggatc acgaagcgga gcacgaagtt cgagcagcga atccgggagc agaccaccac	cgatgtgggc actgatgatt caaaagcggc ttattattgc aaccgttctt agaattgcag cgtgacagtg accctccaaa gcagtggaag	ggctataact tatgatgtga aacaccgcga cagagctggg ggccagccga gcgaacaaaag gcctggaagg caaagcaaca tcccacagaa	caggtcagag atgtgagctg gcaaccgtcc gcctgaccat acattaatca aagccgcacc cgaccctggt cagatagcag acaagtacgc gctacagctg aggcc	gtaccagcag ctcaggcgtg tagcggcctg tgctattgtg gagtgtgacg gtgcctgatt ccccgtcaag ggccagcagc	60 120 180 240 300 360 420 480 540 600 645
<210> 332 <211> 645 <212> DNA <213> Homo	sapiens	•				
tcgtgtacgg catcccggga agcaaccgtt caagcggaag tttggcggcg ctgtttccgc agcgactttt gcgggagtgg tatctgagcc	gtactagcag aggcgccgaa ttagcggatc acgaagcgga gcacgaagtt cgagcagcga atccgggagc agaccaccac	cgatgtgggc actgatgatt caaaagcggc ttattattgc aaccgttctt agaattgcag cgtgacagtg accctccaaa gcagtggaag	ggctataact tatgatgtga aacaccgcga cagagctatg ggccagccga gcgaacaaag gcctggaagg caaagcaaca tcccacagaa	caggtcagag atgtgagctg gcaaccgtcc gcctgaccat actattatga aagccgcacc cgaccctggt cagatagcag acaagtacgc gctacagctg aggcc	gtaccagcag ctcaggcgtg tagcggcctg ttatggtgtg gagtgtgacg gtgcctgatt ccccgtcaag ggccagcagc	60 120 180 240 300 360 420 480 540 600 645

```
<210> 333
<211> 645
<212> DNA
<213> Homo sapiens
<400> 333
gatategtge tgacecagag eeeggegace etgageetgt eteegggega aegtgegace
                                                                        60
ctgagctgca gagcgagcca gagcgtgagc agcagctatc tggcgtggta ccagcagaaa
                                                                       120
ccaggicaag caccgcgict attaatttat ggcgcgagca gccgigcaac iqqqqicccg
                                                                       180
                                                                       240
gegegtttta geggetetgg ateeggeacg gattttacce tgaccattag cageetggaa
cctgaagact ttgcggttta ttattgccag caggctaatg attttcctat tacctttggc
                                                                       300
cagggtacga aagttgaaat taaacgtacg gtggctgctc cgagcgtgtt tatttttccg
                                                                       360
ccqagcqatg aacaactgaa aaqcqgcacg qcqagcqtqg tgtqcctqct gaacaacttt
                                                                       420
tatccgcqtg aagcgaaagt tcaqtggaaa gtagacaacg cgctgcaaag cqccaacagc
                                                                       480
caggaaagcg tgaccgaaca ggatagcaaa gatagcacct attctctgag cagcaccctg
                                                                       540
accctgagca aagcggatta tgaaaaacat aaagtgtatg cgtgcgaagt gacccatcaa
                                                                       600
ggtctgagca gcccggtgac taaatctttt aatcgtggcg aggcc
                                                                       645
<210> 334
<211> 648
<212> DNA
<213> Homo sapiens
<400> 334
qatateqeae tqaeecaqee aqetteaqtq aqeqqeteae cagqteaqaq cattaceate
                                                                        60
tcqtqtacqq qtactagcaq cqatqtqqqc qqctataact atqtqaqctq gtaccaqcaq
                                                                       120
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg
                                                                       180
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
                                                                       240
caagcggaag acgaagcgga ttattattgc cagagctggg acaatcttaa gatgcctgtt
                                                                       300
gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg
                                                                       360
acqctqtttc cqccqaqcaq cqaaqaattq caqqcqaaca aagcqaccct gqtgtqcctq
                                                                       420
attagcgact tttatccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc
                                                                       480
aaggegggag tggagaccac cacaccetee aaacaaagca acaacaagta egeggecage
                                                                       540
agetatetga geetgaegee tgageagtgg aagteeeaca gaagetaeag etgeeaggte
                                                                       600
acgcatgagg ggagcaccgt ggaaaaaacc gttgcgccga ctgaggcc
                                                                       648
<210> 335
<211> 648
<212> DNA
<213> Homo sapiens
<400> 335
gatategeae tgacceagee agetteagtg ageggeteae caggteagag cattaceate
                                                                        60
tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag
                                                                       120
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg
                                                                       180
                                                                       240
ageaaccgtt ttageggate caaaagegge aacacegega geetgaceat tageggeetg
caageggaag acgaagegga ttattattge cagagetatg acgtttttcc tattaategt
                                                                       300
gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg
                                                                       360
                                                                       420
acgctgtttc cgccgagcag cgaagaattg caggcgaaca aagcgaccct ggtgtgcctg
attagegact tttateeggg ageegtgaca gtggeetgga aggeagatag eageeeegte
                                                                       480
```

aaggegggag tggagaceae cacaceetee aaacaaagea acaacaagta egeggeeage agetatetga geetgaegee tgageagtgg aagteeaca gaagetacag etgeeaggte aegeatgagg ggageacegt ggaaaaaace gttgegeega etgaggee	540 600 648
<210> 336 <211> 639 <212> DNA <213> Homo sapiens	
<pre><400> 336 gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg caagcggaag acgaagcgga ttattattgc cagagcgatc tttatttcc tgtgtttggc ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac ttttatccgg gagccgtgac agtggcctgg aacgacgata gcagccccgt caaggcgga gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg agcctgacgc ttggaaaaaac cgttgcgccg actgaggcc</pre>	60 120 180 240 300 360 420 480 540 600 639
<210> 337 <211> 642 <212> DNA <213> Homo sapiens	
<pre><400> 337 gatategeac tgacccagec agetteagtg ageggeteac caggteagag cattaceate tegtgtacgg gtactageag egatgtggge ggetataact atgtgagetg gtaccageag cateceggga agegecegaa actgatgatt tatgatgtga geaacegtee etcaggegtg ageacegtt ttageggate caaaagegge aacacegega geetgaceat tageggeetg caageggaag acgaagegga ttattattge eageegaaag eegeacegag tgtgaegetg tteegeega geagegaaga atgeaggeg aacaaagega eeetggtgg gaettttate egggageegt gaeagtggee tggaaggeag atageagee eetgagegg ggagtggaga eeecacaee etceaaaeaa ageaaeaea agtaegegge eageagetat etgageetga egeetgagea gtggaagtee eacagaaget acagetgeea ggegggagaa eegtggaaga eegtggaaaa aacegttgeg eegaetgagg</pre>	60 120 180 240 300 360 420 480 540 600 642
<210> 338 <211> 636 <212> DNA <213> Homo sapiens	
<400> 338 gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc tcgtgtagcg gcgatgcgct gggcgataaa tacgcgagct ggtaccagca gaaacccggg caggcgccag ttctggtgat ttatgatgat tctgaccgtc cctcaggcat cccggaacgc tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa	60 120 180 240

```
300
gacgaagcgg attattattg ccagagccgt gaccetgttg gttttcctgt gtttggcggc
                                                                       360
ggcacgaagt taaccgttct tggccagccg aaagccgcac cgagtgtgac gctgtttccg
ccgagcagcg aagaattgca ggcgaacaaa gcgaccctgg tgtgcctgat tagcgacttt
                                                                       420
                                                                       480
tatccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg
                                                                       540
qaqaccacca caccetecaa acaaagcaac aacaagtacg cggccagcag etatetgage
                                                                       600
ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgagggg
                                                                       636
agcaccgtgg aaaaaaccgt tgcgccgact gaggcc
<210> 339
<211> 642
<212> DNA
<213> Homo sapiens
<400> 339
gatategeac tgacceagec agetteagtg ageggeteac caggteagag cattaceate
                                                                        60
                                                                       120
tcqtqtacqq qtactaqcaq cgatqtqqqc qgctataact atgtqagctg gtaccagcag
                                                                       180
catcccqqqa aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg
                                                                       240
aqcaaccqtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
caageggaag acgaagegga ttattattge cagagetatg acetttetee tegtgtgttt
                                                                       300
qqcqqcqqca cqaaqttaac cqttcttqqc caqccqaaaq ccqcaccqaq tqtqacqctq
                                                                       360
tttccgccga gcagcgaaga attgcaggcg aacaaagcga ccctggtgtg cctgattagc
                                                                       420
gacttttatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg
                                                                       480
ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat
                                                                       540
ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat
                                                                       600
gaggggagca ccgtggaaaa aaccgttgcg ccgactgagg cc
                                                                       642
<210> 340
<211> 648
<212> DNA
<213> Homo sapiens
<400> 340
                                                                        60
gatategeae tgacecagee agetteagtg ageggeteae caggteagag cattaceate
                                                                       120
tcqtqtacqq qtactaqcaq cqatqtqqqc ggctataact atgtgagctg gtaccagcag
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg
                                                                       180
                                                                       240
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
                                                                       300
caageggaag acgaagegga ttattattge cagagetatg acttttetea ttatttttt
                                                                       360
gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg
acgctgtttc cgccgagcag cgaagaattg caggcgaaca aagcgaccct ggtgtgcctg
                                                                       420
attagcgact tttatccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc
                                                                       480
aaggegggag tggagaccac cacaccctcc aaacaaagca acaacaagta cgeggecage
                                                                       540
                                                                       600
aqctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc
                                                                       648
acqcatgagg ggagcaccgt ggaaaaaacc gttgcgccga ctgaggcc
<210> 341
<211> 636
<212> DNA
<213> Homo sapiens
<400> 341
```

gatatcgaac tgacccagcc tcgtgtagcg gcgatgcgct caggcgccag ttctggtgat tttagcggat ccaacagcgg gacgaagcgg attattattg ggcacgaagt taaccgttct ccgagcagcg aagaattgca tatccgggag ccgtgacagt gagaccacca caccctccaa ctgacgctg agcagtggaa agcaccgtgg aaaaaaccgt	gggcgataaa ttatgatgat caacacegcg ccagagctat tggccagccg ggcgaacaaa ggcctggaag acaaagcaac gtcccacaga	tacgcgagct tctgaccgtc accctgacca gaccttcgtt aaagccgcac gcgaccctgg gcagatagca aacaagtacg agctacagct	ggtaccagca cctcaggcat ttagcggcac attctcatgt cgagtgtgac tgtgcctgat gccccgtcaa cggccagcag	gaaacccggg cccggaacgc tcaggcggaa gtttggcggc gctgtttccg tagcgacttt ggcgggagtg ctatctgagc	60 120 180 240 300 360 420 480 540 600 636
<211> 642 <212> DNA <213> Homo sapiens					
<400> 342					
gatatogoac tgacccagec	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg gtactagcag					120
catecegga aggegeegaa					180
agcaaccgtt ttagcggatc					240
caageggaag aegaagegga					300
ggcggcggca cgaagttaac					360
tttccgccga gcagcgaaga	attgcaggcg	aacaaagcga	ccctggtgtg	cctgattagc	420
gacttttatc cgggagccgt	gacagtggcc	tggaaggcag	atagcagccc	cgtcaaggcg	480
ggagtggaga ccaccacac	ctccaaacaa	agcaacaaca	agtacgcggc	cagcagctat	540
ctgageetga egeetgagea				ggtcacgcat	600
gaggggagca ccgtggaaaa	aaccgttgcg	ccgactgagg	cc		642
<210> 343 <211> 645 <212> DNA <213> Homo sapiens					
<400> 343					
gatategeae tgaeecagee	agcttcagtg	agcggctcac	caggtcagag	cattaccatc	60
tcgtgtacgg gtactagcag	cgatgtgggc	ggctataact	atgtgagctg	gtaccagcag	120
cateceggga aggegeegaa					180
agcaaccgtt ttagcggato	caaaagcggc	aacaccgcga	gcctgaccat	tagcggcctg	240
caagcggaag acgaagcgga	ttattattgc	cagagctatg	actttactta	tggttctgtg	300
tttggcggcg gcacgaagtt	aaccgttctt	ggccagccga	aagccgcacc	gagtgtgacg	360
ctgtttccgc cgagcagcga					420
agegaetttt atcegggage					480
gcgggagtgg agaccaccac					540
tatctgagcc tgacgcctga				ccaggtcacg	600
catgagggga gcaccgtgga	aaaaaccgtt	gcgccgactg	aggcc		. 645
<210> 344					

<210> 344 <211> 645

```
<212> DNA
<213> Homo sapiens
<400> 344
gatategtge tgacceagag eceggegace etgageetgt eteegggega aegtgegace
ctgagctgca gagcgagcca gagcgtgagc agcagctatc tggcgtggta ccagcagaaa
                                                                       120
ccaggtcaag caccgcgtct attaatttat ggcgcgagca gccgtgcaac tggggtcccg
                                                                       180
gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa
                                                                       240
cctgaagact ttgcggttta ttattgccag cagtttaatg attctcctta tacctttggc
                                                                       300
cagggtacga aagttgaaat taaacgtacg gtggctgctc cgagcgtgtt tatttttccg
                                                                       360
                                                                       420
ccgagcgatg aacaactgaa aagcggcacg gcgagcgtgg tgtgcctgct gaacaacttt
                                                                       480
tatccgcgtg aagcgaaagt tcagtggaaa gtagacaacg cgctgcaaag cggcaacagc
caggaaageg tgaccgaaca ggatagcaaa gatagcacct attctctgag cagcaccctg
                                                                       540
                                                                       600
accetgagea aageggatta tgaaaaacat aaagtgtatg egtgegaagt gacceateaa
ggtctgagca gcccggtgac taaatctttt aatcgtggcg aggcc
                                                                       645
<210> 345
<211> 649
<212> DNA
<213> Homo sapiens
<400> 345
ggccgatatc gcactgaccc agccagcttc agtgagcggc tcaccaggtc agagcattac
                                                                        60
catctcgtgt acgggtacta gcagcgatgt gggcggctat aactatgtga gctggtacca
                                                                       120
gcagcatccc gggaaggcgc cgaaactgat gatttatgat gtgagcaacc gtccctcagg
                                                                       180
                                                                       240
cqtqaqcaac cqttttaqcq gatccaaaag cggcaacacc gcgagcctga ccattagcgg
                                                                       300
cctgcaagcg gaagacgaag cggattatta ttgccagagc tatgacattt ctggttatcc
                                                                       360
tgtgtttggc ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt
gacgctgttt ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct
                                                                       420
gattagcgac ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagcccgt
                                                                       480
caaggeggga gtggagacca ccacaccete caaacaaage aacaacaagt acgeggecag
                                                                       540
cagctatctg agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt
                                                                       600
cacgcatgag gggagcaccg tggaaaaaac cgttgcgccg actgaggcc
                                                                       649
<210> 346
<211> 648
<212> DNA
<213> Homo sapiens
<400> 346
                                                                        60
gatatcgcac tgacccagcc agettcagtg agcggctcac caggtcagag cattaccatc
                                                                       120
tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag
                                                                       180
catcecggga aggegecgaa actgatgatt tatgatgtga geaaccgtee etcaggegtg
                                                                       240
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
caagcggaag acgaagcgga ttattattgc cagagccgtg acctttatta tgtttattat
                                                                       300
gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg
                                                                       360
                                                                       420
acqctqtttc cgccqagcag cgaagaattg caggcgaaca aagcgaccct ggtgtgcctg
attagegact tttateeggg ageegtgaca gtggeetgga aggeagatag cageeeegte
                                                                       480
aaggegggag tggagaceae cacaceetee aaacaaagea acaacaagta egeggeeage
                                                                       540
agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc
                                                                       600
```

acgcatgagg ggagcaccgt	ggaaaaaacc	gttgcgccga	ctgaggcc		648
<210> 347 <211> 633 <212> DNA <213> Homo sapiens					
<400> 347 gatatcgaac tgacccagcc tcgtgtagcg gcgatgcgct caggcgccag ttctggtgat tttagcggat ccaacagcgg gacgaagcga attattattg acgaagttaa ccgttcttgg agcagcgaag aattgcaggc ccgggagccg tgacagtggc accaccacac cctccaaaca acgcctgagc agtggaagtc accgtggaaa aaaccgttgc	gggcgataaa ttatgatgat caacaccgcg ccagagctat ccagccgaaa gaacaaagcg ctggaaggca aagcaacaac ccacagaagc	tacgcgagct tctgaccgtc accctgacca gaccgttcta gccgcaccga accctggtgt gatagcagcc aagtacgcgg tacagctgcc	ggtaccagca cetcaggcat ttagcggcac tgtgggtgtt gtgtgacgct gcctgattag ccgtcaaggc ccagcagcta	gaaacccggg cccggaacgc tcaggcggaa tggcggcggc gtttccgccg cgacttttat gggagtggag tctgagcctg	60 120 180 240 300 360 420 480 540 600 633
<210> 348 <211> 645 <212> DNA <213> Homo sapiens					
<pre><400> 348 gatatcgcac tgacccagcc tcgtgtacgg gtactagcag catcccggga aggcgccgaa agcaaccgtt ttagcggatc caagcggaag acgaagcgga tttggcggcg gcacgaagtt ctgttccgc cgagcagcga agcgacttt atccgggagc gcgggagtgg agaccaccac tatctgagcc tgacgcctga</pre>	cgatgtgggc actgatgatt caaaagcggc ttattattgc aaccgttctt agaattgcag cgtgacagtg accctccaaa gcagtggaag	ggctataact tatgatgtga aacaccgcga cagagctggg ggccagccga gcgaacaaag gcctggaagg caaagcaaca tcccacagaa	atgtgagctg gcaaccgtcc gcctgaccat acgttcagac aagccgcacc cgaccctggt cagatagcag acaagtacgc gctacagctg	gtaccagcag ctcaggcgtg tagcggcctg tgataaggtg gagtgtgacg gtgcctgatt ccccgtcaag ggccagcagc	60 120 180 240 300 360 420 480 540 600 645
<210> 349 <211> 636 <212> DNA <213> Homo sapiens					
<pre><400> 349 gatatcgaac tgacccagcc tcgtgtagcg gcgatgcgct caggcgccag ttctggtgat tttagcggat ccaacagcgg gacgaagcgg attattattg ggcacgaagt taaccgttct</pre>	gggcgataaa ttatgatgat caacaccgcg ccagagctgg	tacgcgagct tctgaccgtc accctgacca gacccttctc	ggtaccagca cctcaggcat ttagcggcac attattatgt	gaaacccggg cccggaacgc tcaggcggaa gtttggcggc	60 120 180 240 300 360

tatccgggag gagaccacca ctgacgcctg	aagaattgca ccgtgacagt caccctccaa agcagtggaa aaaaaaccgt	ggcctggaag acaaagcaac gtcccacaga	gcagatagca aacaagtacg agctacagct	gccccgtcaa	ggcgggagtg ctatctgagc	420 480 540 600 636
<210> 350 <211> 645 <212> DNA <213> Homo	sapiens	÷				
tcgtgtacgg catcccggga agcaaccgtt caagcggaag tttggcggcg ctgtttccgc agcgactttt gcgggagtgg tatctgagcc	tgacccagcc gtactagcag aggcgccgaa ttagcggatc acgaagcga gcacgaagtt cgagcagcga atccgggagc agaccaccac tgacgcctga gcaccgtgga	cgatgtgggc actgatgatt caaaagcggc ttattattgc aaccgttctt agaattgcag cgtgacagtg accctccaaa gcagtggaag	ggctataact tatgatgtga aacaccgcga cagagctatg ggccagccga gcgaacaaag gcctggaagg caaagcaaca tcccacagaa	atgtgagctg gcaaccgtcc gcctgaccat acattatgcc aagccgcacc cgaccctggt cagatagcag acaagtacgc gctacagctg	gtaccagcag ctcaggcgtg tagcggcctg tgagcgtgtg gagtgtgacg gtgcctgatt ccccgtcaag ggccagcagc	60 120 180 240 300 360 420 480 540 600 645
<210> 351 <211> 645 <212> DNA <213> Homo	sapiens					
tcgtgtacgg catcccggga agcaaccgtt caagcggaag tttggcggcg ctgtttccgc agcgactttt gcgggagtgg tatctgagcc	aggcgccgaa ttagcggatc acgaagcgga gcacgaagtt cgagcagcga atccgggagc agaccaccac	cgatgtgggc actgatgatt caaaagcggc ttattattgc aaccgttctt agaattgcag cgtgacagtg accctccaaa gcagtggaag	ggctataact tatgatgtga aacaccgcga cagagcatgg ggccagccga gcgaacaaag gcctggaagg caaagcaaca tcccacagaa	atgtgagctg gcaaccgtcc gcctgaccat actttcgtct aagccgcacc cgaccctggt cagatagcag acaagtacgc gctacagctg	gtaccagcag ctcaggcgtg tagcggcctg tatgcatgtg gagtgtgacg	60 120 180 240 300 360 420 480 540 600 645
<210> 352 <211> 645 <212> DNA <213> Homo	sapiens		·			
<400> 352 gatategeac tegtgtaegg	tgacccagcc gtactagcag	agcttcagtg cgatgtgggc	ageggeteae ggetataaet	caggtcagag atgtgagctg	cattaccatc gtaccagcag	60 120

```
180
catcccqqqa aggcqccqaa actqatqatt tatqatgtga gcaaccgtcc ctcaggcgtg
                                                                       240
agcaaccqtt ttagcqqatc caaaaqcgqc aacaccgcga gcctgaccat tagcggcctg
                                                                       300
caageggaag acgaagegga ttattattge cagagetttg acatgattea teettatgtg
                                                                       360
tttggcggcg gcacgaagtt aaccgttctt ggccagccga aagccgcacc gagtgtgacg
ctgtttccgc cgagcagcga agaattgcag gcgaacaaag cgaccctggt gtgcctgatt
                                                                       420
                                                                       480
agcqactttt atccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag
gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc
                                                                       540
tatctgagec tgacgectga geagtggaag teccacagaa getacagetg ecaggteacg
                                                                       600
catgagggga gcaccgtgga aaaaaccgtt gcgccgactg aggcc
                                                                       645
<210> 353
<211> 639
<212> DNA
<213> Homo sapiens
<400> 353
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc
                                                                        60
tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag
                                                                       120
cateceggga aggegeegaa actgatgatt tatgatgtga geaacegtee eteaggegtg
                                                                       180
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
                                                                       240
caagcggaag acgaagcgga ttattattgc cagagcgact ttcctgttat ggtgtttggc
                                                                       300
ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt
                                                                       360
ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac
                                                                       420
ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga
                                                                       480
                                                                       540
qtqqaqacca ccacacctc caaacaaagc aacaacaagt acgcggccag cagctatctg
                                                                       600
agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag
                                                                       639
gggagcaccg tggaaaaaac cgttgcgccg actgaggcc
<210> 354
<211> 639
<212> DNA
<213> Homo sapiens
<400> 354
                                                                        60
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc
tcgtgtacgg gtactagcag cgatgtgggc ggctataact atgtgagctg gtaccagcag
                                                                       120
                                                                       180
catcccggga aggcgccgaa actgatgatt tatgatgtga gcaaccgtcc ctcaggcgtg
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
                                                                       240
caagcggaag acgaagcgga ttattattgc cagagcgaca atccttatct tgtgtttggc
                                                                       300
                                                                       360
ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt
                                                                       420
ccqccqaqca qcqaaqaatt qcaggcgaac aaagcgaccc tggtgtgcct gattagcgac
                                                                       480
ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga
                                                                       540
gtggagacca ccacacctc caaacaaagc aacaacaagt acgcggccag cagctatctg
agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag
                                                                       600
                                                                       639
gggagcaccg tggaaaaaac cgttgcgccg actgaggcc
<210> 355
<211> 10
<212> PRT
```

<213> Homo sapiens

```
<400> 355
Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5
<210> 356
<211> 10
<212> PRT
<213> Homo sapiens
<400> 356
Gly Phe Thr Phe Asn Ser Tyr Ala Met Ser
            5
<210> 357
<211> 17
<212> PRT
<213> Homo sapiens
<400> 357
Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
                5
                                   10
Gly
<210> 358
<211> 17
<212> PRT
<213> Homo sapiens
<400> 358
Val Ile Ser Gly Asn Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1
                                   10
Gly
<210> 359
<211> 17
<212> PRT
<213> Homo sapiens
Gly Ile Ser Gly Asn Gly Val Leu Ile Phe Tyr Ala Asp Ser Val Lys
                                   10
1
Gly
<210> 360
<211> 5
<212> PRT
```

```
<213> Homo sapiens
<400> 360
Gly Leu Met Asp Tyr
<210> 361
<211> 4
<212> PRT
<213> Homo sapiens
<400> 361
Trp Phe Asp His
. 1
<210> 362
<211> 4
<212> PRT
<213> Homo sapiens
<400> 362
Trp Phe Asp Val
<210> 363
<211> 14
<212> PRT
<213> Homo sapiens
<400> 363
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
                5
                                  10
<210> 364
<211> 7
<212> PRT
<213> Homo sapiens
<400> 364
Asp Val Ser Asn Arg Pro Ser
     5
<210> 365
<211> 9
<212> PRT
<213> Homo sapiens
<400> 365
Gln Ser Tyr Asp Phe Ile Arg Phe Met
                5
```

```
<210> 366
 <211> 10
<212> PRT
 <213> Homo sapiens
 <400> 366
 Gly Gly Thr Phe Ser Ser Tyr Ala Ile Ser
 <210> 367
 <211> 10
 <212> PRT
 <213> Homo sapiens
 <400> 367
 Gly Tyr Ser Phe Thr Ser Tyr Trp Ile Gly
                5
 <210> 368
 <211> 17
 <212> PRT
 <213> Homo sapiens
 <400> 368
 Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
      5
 Gly
 <210> 369
 <211> 17
 <212> PRT
 <213> Homo sapiens
 <400> 369
 Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
 1 5
                                   10
 Gly
 <210> 370
 <211> 16
 <212> PRT
 <213> Homo sapiens
 <400> 370
 Trp Ser Asp Gln Ser Tyr His Tyr Tyr Trp His Pro Tyr Phe Asp Val
                5
                                   10
```

```
<210> 371
<211> 13
<212> PRT
<213> Homo sapiens
<400> 371
Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Tyr Val Ser
<210> 372
<211> 14
<212> PRT
<213> Homo sapiens
<400> 372
Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                                    10
<210> 373
<211> 11
<212> PRT
<213> Homo sapiens
<400> 373
Leu Met Ile Tyr Asp Asn Asn Gln Arg Pro Ser
<210> 374
<211> 11
<212> PRT
<213> Homo sapiens
<400> 374
Leu Met Ile Tyr Asp Val Ser Asn Arg Pro Ser
1 5
<210> 375
<211> 11
<212> PRT
<213> Homo sapiens
<400> 375
Leu Met Ile Tyr Ala Gly Asn Asn Arg Pro Ser
               5
<210> 376
<211> 10
<212> PRT
<213> Homo sapiens
```

WO 02/086085

```
<400> 376
Gln Ala Phe Asp Val Ala Pro Asn Gly Lys
               5
<210> 377
<211> 10
<212> PRT
<213> Homo sapiens
<400> 377
Gln Ala Phe Ala Val Met Pro Asn Val Glu
                5
<210> 378
<211> 10
<212> PRT
<213> Homo sapiens
<400> 378
Gln Ser Phe Thr Val Ser Pro Gly Ala Asp
<210> 379
<211> 9
<212> PRT
<213> Homo sapiens
<400> 379
Gln Ala Tyr Asp Ser Ser Gly Tyr Pro
<210> 380
<211> 17
<212> DNA
<213> Homo sapiens
<400> 380
                                                                        17
gtggtggttc cgatatc
<210> 381
<211> 43
<212> DNA
<213> Homo sapiens
<400> 381
                                                                        43
agcgtcacac tcggtgcggc tttcggctgg ccaagaacgg tta
```

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

□ BLACK BORDERS
□ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
□ FADED TEXT OR DRAWING
□ BLURRED OR ILLEGIBLE TEXT OR DRAWING
□ SKEWED/SLANTED IMAGES
□ COLOR OR BLACK AND WHITE PHOTOGRAPHS
□ GRAY SCALE DOCUMENTS
□ LINES OR MARKS ON ORIGINAL DOCUMENT
□ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

IMAGES ARE BEST AVAILABLE COPY.

☐ OTHER:

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.